FUNCTIONAL MEDICINE
Continuing Education

Case-Based Functional Medicine Approach to IBS/IBD

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Disclosures

- Lara Zakaria does not report any actual or potential conflicts of interest in relation to this continuing pharmacy education course.
- Dr. Hartzler reports she is the owner of PharmToTable, LLC.

Objectives

1. Distinguish between the signs, symptoms, and complications of IBS vs. IBD
2. Compare and contrast inflammatory components of both IBS and IBD
3. Develop a therapeutic plan for IBS/IBD patients

Global Prevalence of Irritable Bowel Syndrome (IBS)

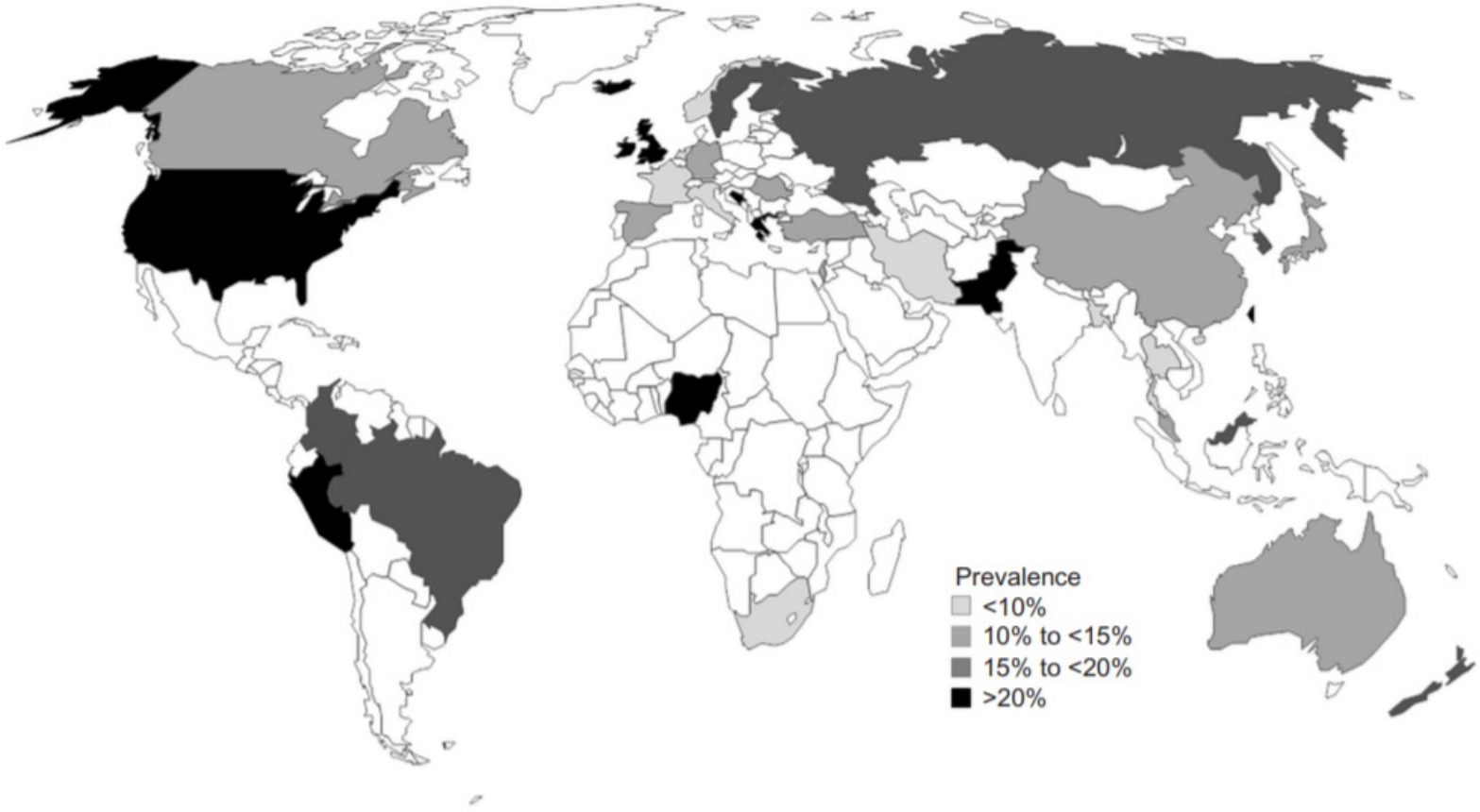

Figure 1 Worldwide prevalence of irritable bowel syndrome, as reported by country.

Clin Epidemiol. 2014;6:71-80. Published 2014 Feb 4.

Global Prevalence of Inflammatory Bowel Disease (IBD)

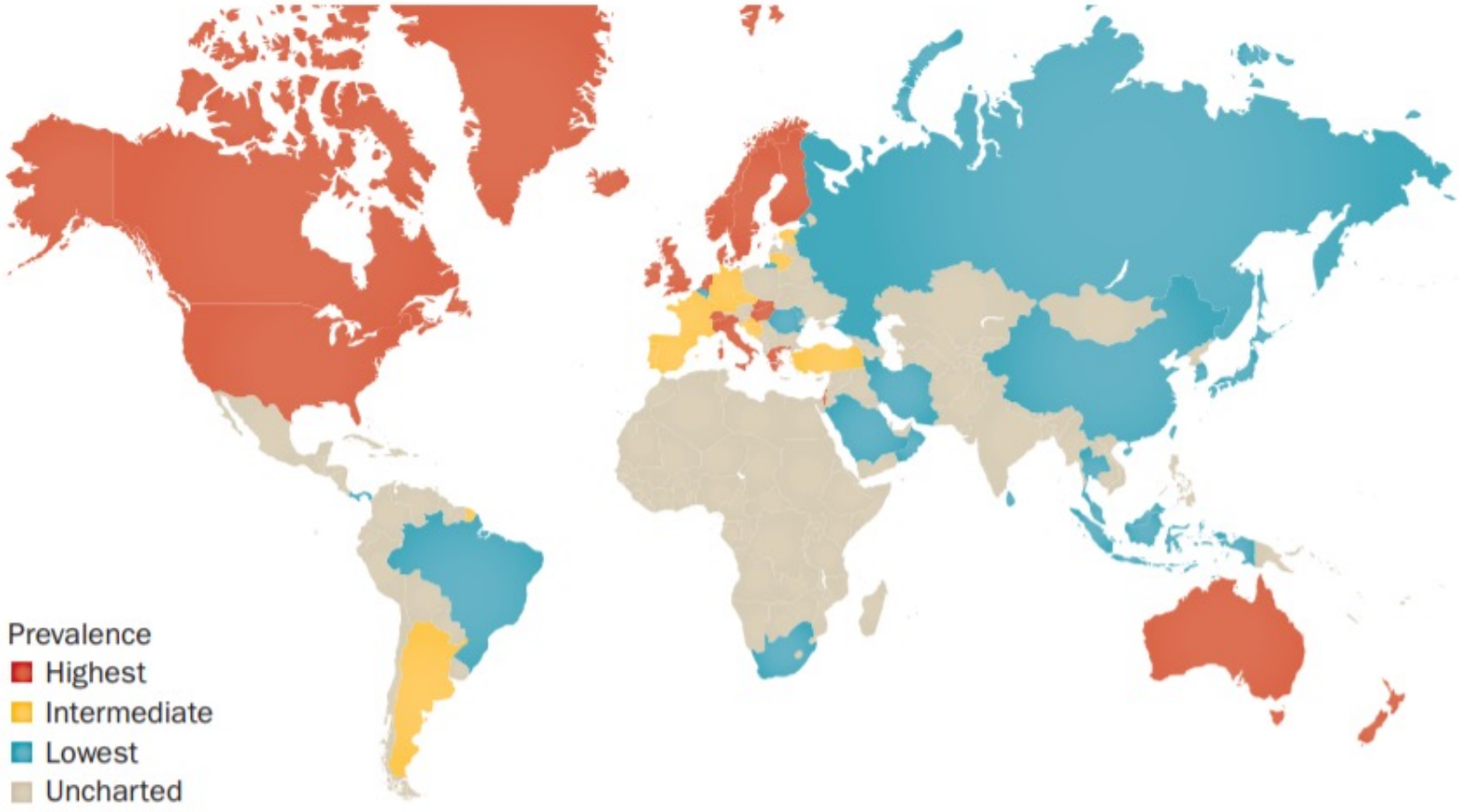

Figure 2 | The global prevalence of IBD in 2015. Data from Molodecky *et al.*[4] Adapted from an image provided by PresenterMedia.

Nat Rev Gastroenterol Hepatol. 2015;12(12):720-727

Irritable Bowel Syndrome (IBS)

Irritable Bowel Syndrome (IBS)

A complex, chronic disorder characterized by abdominal pain or discomfort and altered bowel habits.

No anatomically abnormality

Gut – brain axis

May impact up to 20% of US population

Clin Epidemiol. 2014;6:71-80. Published 2014 Feb 4.


Gutsy move
...for a brain!

AP&T Alimentary Pharmacology and Therapeutics

Evidence that independent gut-to-brain and brain-to-gut pathways operate in the irritable bowel syndrome and functional dyspepsia: a 1-year population-based prospective study

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SUMMARY

Background
Traditionally, functional gastrointestinal disorders (FGIDs) are c
alised as originating in the brain via stress pathways (brain-to-g
uncertain how many with irritable bowel syndrome (IBS) and f
dyspepsia (FD) have a gut origin of symptoms (gut-to-brain pathw

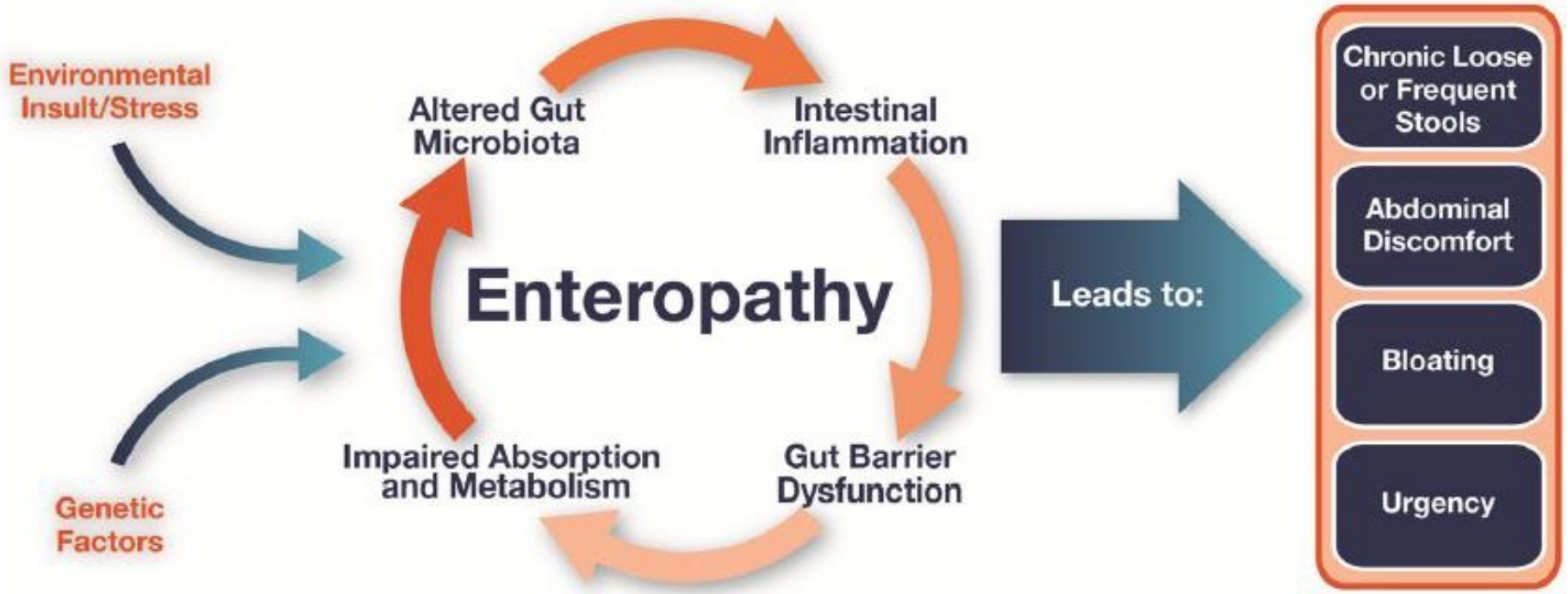
Aims
To determine if there is a distinct brain-to-gut FGID (where psyc
symptoms begin first) and separately a distinct gut-to-brain FGI
gut symptoms start first).

Methods
A prospective random population sample from Newcastle, Austra
responded to a validated survey in 2012 and completed a 1-year follo
survey (n = 1900). The surveys contained questions on Rome III IBS and FD and the Hospital Anxiety and Depression Scale.

Results
We found that higher levels of anxiety and depression at baseline were significant predictors of developing IBS (OR = 1.31; 95% CI 1.06–1.61, P = 0.01; OR = 1.54; 95% CI 1.29–1.83, P < 0.001) and FD (OR = 1.28; 95% CI 1.05–1.55, P = 0.01; OR = 1.55, 95% CI 1.32–1.83, P < 0.001), respectively, at the 1-year follow-up. Among those people who did *not* have elevated levels of anxiety and depression at baseline, subjects at baseline with documented IBS (mean difference 0.34; 95% CI 0.13–0.55, P = 0.002; 0.81; 95% CI 0.47–1.15, P < 0.001) and FD (0.38; 95% CI 0.14–0.63, P = 0.002; 0.92; 95% CI 0.57–1.27, P < 0.001), reported significantly higher levels of anxiety and depression at the 1-year follow-up. We calculated in one-third of individuals a mood disorder precedes FGID but in two-thirds an FGID precedes the mood disorder.

Conclusion
While brain–gut pathways are bidirectional, a major subset begin with gut symptoms first and only then psychological distress develops, implicating primary gut mechanisms as drivers of the gut and extra-intestinal features in many cases.

In conclusion, ***this study provides further strong evidence that the gut and brain interact bidirectionally in IBS and FD*** *and extends past work to a shorter timescale. The data also confirm that there is a subset with FD and IBS that have their disorder begin in the gut and the gut may primarily drive psychological alterations in some with FGIDs.*



Dig Dis Sci (2015) 60:13–23

IBS Patient Evaluation

- Patient history is the most important component of a diagnosis of IBS since there are no physical exam findings
- Absence of physical exam findings
- Rome III classification
- Constipation from IBS = pain
- A history of weight loss, nocturnal awakening of diarrhea or abdominal pain, anemia, or rectal bleeding should be referred out for an alternative diagnosis

Rome Criteria for IBS

Rome III Criteria	Recurrent abdominal pain or discomfort at least 3 days/month in the last 3 months associated with two or more of the following: • Improvement with defecation • Onset associated with a change in frequency of stool • Onset associated with a change in form (appearance) of stool [a]Criterion fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis. [b]"Discomfort" means an uncomfortable sensation not described as pain.
Rome IV Criteria	Recurrent abdominal pain, on average, at least 1 day/week in the last 3 months, associated with two or more of the following criteria: • Related to defecation • Associated with a change in frequency of stool • Associated with a change in form (appearance) of stool. [c]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

https://irritablebowelsyndrome.net/clinical/new-rome-iv-diagnostic-criteria/

Rome Criteria for IBS: Subgroups

- Constipation predominant IBS (IBS-C)
- Diarrhea predominant IBS (IBS-D)
- Mixed (IBS-M)

SUBTYPE	STOOL TYPE 1 & 2	STOOL TYPE 6 & 7
IBS with predominant constipation	More than 25%	Less than 25%
IBS with predominant diarrhea	Less than 25%	More than 25%
IBS with mixed bowel habits	More than 25%	More than 25%

IBS Unclassified: Patient who meets diagnostic criteria for IBS but whose bowel habits cannot be accurately categorized into one of the three subtypes above.

Source: Lacy BE, et al. Bowel Disorders. Gastroenterology. 2016;150:1393-1407.

Pathophysiology

- Visceral Hypersensitivity
- Disordered cortical pain processing
- Increased intestinal permeability
- Small bowel intestinal overgrowth (SIBO)

IBS & Comorbid Disorders

- Fibromyalgia
- Chronic Fatigue Syndrome
- Chronic pelvic pain
- Cystitis
- Migraines
- Up to 94% of IBS have psychiatric illness
- IBS is not a psychiatric disorder but a disorder of the brain-gut axis

Visceral Hypersensitivity

Impacts 2/3 of patients with IBS

Low threshold to painful stimuli from the GI tract

Mechanisms

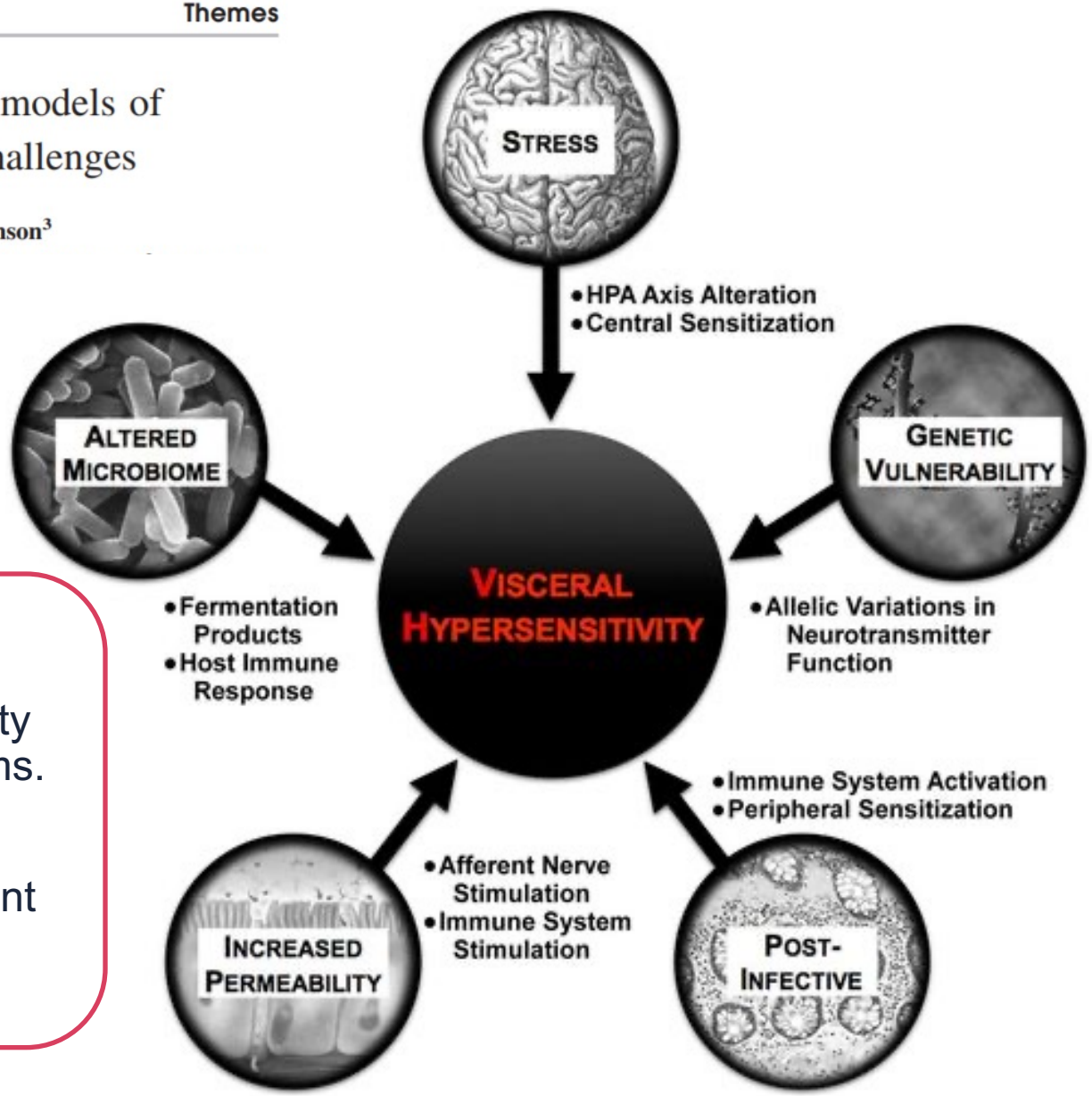
- **Peripheral sensitization**
  - Inflammatory mediators up-regulate sensitivity of nociceptor
  - terminals
  - Serotonin, bradykinin, tachykinans, calcitonin gene-related peptide (CGRP), neurotropins
  - 95% of serotonin is in the gut
- **Central sensitization**
  - Increased sensitivity of spinal neurons
  - Alterations in a cognitive response

Am J Physiol Gastrointest Liver Physiol 308: G885–G903, 2015.
First published March 12, 2015; doi:10.1152/ajpgi.00463.2014.

Animal models of gastrointestinal and liver diseases. Animal models of visceral pain: pathophysiology, translational relevance, and challenges

Beverley Greenwood-Van Meerveld,[1,2,3] Dawn K. Prusator,[3] and Anthony C. Johnson[3]

Mechanisms of visceral hypersensitivity. Combined evidence from animal models and clinical studies supports the hypothesis that visceral hypersensitivity is due to multiple central and peripheral mechanisms. Interactions between each mechanism (i.e., stress changes permeability, which can alter microbiota, leading to immune activation) make the development of adequate therapies a continuing challenge for future research.



Am J Physiol Gastrointest Liver Physiol. 2015 Jun 1;308(11):G885-903

Enterochromaffin cells & Serotonin in Altered GI Motility

Release 5-HTP after meals

- 5-HTP binds 5-HT4 receptors which control GI motility and secretion

Alterations in 5-HTP production, serotonin reuptake or metabolism

- Leads to alterations in visceral motility, secretion, and sensation
- ***Increased 5-HTP implicated in IBS-D***
- ***Reduced 5-HTP implicated in IBS-C***

Studies on post-infections IBS (PI-IBS)

- Increased number of EC cells in post-infectious IBS
- Increased # of EC cells → increased circulating 5-HTP

Increased Intestinal Permeability

Post-infectious IBS (PI-IBS) → inflammatory triggered inflammation by infection

More common among IBS-D patients, *especially those with a history of atopy*

Can have an inflammatory component for those with PI-IBS or IBS-D

Increased number of mast cells and activated T-lymphocytes of patients with IBS-D

Small Intestinal Bacteria Overgrowth (SIBO)

~10% of IBS patients (wide variety in the literature)

Diagnosis is usually with breath tests (controversial)

Can exacerbate IBS symptoms (Bloating, cramping, diarrhea)

Symptoms caused by malabsorption of ingested fat, protein, and especially carbohydrates

IBS Evaluation *(additional considerations)*

A history of weight loss, nocturnal awakening of diarrhea or abdominal pain, anemia, or rectal bleeding should be referred out for an alternative diagnosis

Serum laboratory tests in IBS are typically normal

Rule out underlying issues (thyroid, celiac)

Functional testing panels

- Food antibody testing
- Organic acid testing
- Stool testing- rule of infection in those with diarrhea.
- Lactulose hydrogen breath test (SIBO)

IBS Evaluation *(continued)*

Organic Acids (OAT)

- Evaluate serotonin levels since its main output is from the digestive tract.
- Urinary excretion of 5-hydroxyindolic acetic acid (5-HIAA) using organic acid testing
- Low levels of 5-HIAA are associated with low total body serotonin production
- Evaluate catecholamine levels by monitoring the urinary excretion of the metabolites vanillmandelate (VMA) and homovanilate (HVA) using organic acid testing.
- Elevated levels of these metabolites may be associated with excessive catecholamine excretion and with clinical states anxiety and IBS.

Stool testing

- Rule out organic bowel disease and microbial issues (dysbiosis).
- Molecular DNA-based techniques are now available and provide comprehensive evaluation of GI microbiota and markers of GI inflammation and absorption/digestive functionality

Irritable Bowel Disease (IBD)

Irritable Bowel Syndrome

- Characterized by unremitting intestinal inflammation
- Includes tissue injury caused by oxidative and metabolic stress
- Genetic susceptibility with environmental and autoimmune triggers
- Includes Ulcerative Colitis (UC) and Crohn’s Disease (CD)

Pathophysiology

- Tissue damage to the intestinal lining
- Malnutrition
- Growth retardation
- Nutrient deficiencies
- Chronic Inflammation

IBD: Symptoms

- Chronic diarrhea
- Abdominal pain
- Weight loss
- Nutritional deficiencies (specifically B12, lipid soluble vitamins)

IBD: Diagnostic Criteria

CBC to assess inflammation and nutritional deficiencies

Elevated calprotectin levels

Endoscopy to assess tissue damage in the colon

Chronic diarrhea

Classified by location of the disease

- Crohn's Disease (any part of the digestive track)
- Ulcerative Colitis (large intestines/colon)

IBD Evaluation

Inflammation and disease activity

- Hs-CRP/CRP
- Sed rate
- Vitamin D 25-OH; 1,25 dihydroxyvitamin D

Anemia

- CBC w/diff
- Iron Panel
- Vitamin B12 or MMA, Folate

Metabolic profile

- Lipid Panel
- Fasting blood sugar
- HbA1c
- Insulin

Hydration

- Management of fluid and electrolytes for adequate hydration
- Vital signs, CBC w/diff, CMP-14

Diagnostic Criteria: UC vs CD

Crohn's Disease

- Transmural inflammation and may affect any part of the colon.
- Cobbled mucosa (evidence of aphthous ulcerations)
- Mucosal changes in the ileum (Assessed via endoscopy)

Ulcerative Colitis

- Affects the colonic mucosa
- Inflammation at the rectum

Initial Functional Assessment

Multi-profile panel

- A comprehensive assessment including organic acids, amino acids, and oxidative stress markers; assists in detecting individual etiopathologenic factors and in individualizing treatment plans.

Food-specific IgG antibodies

- Food reactions have been associated with inflammation. Multiple IgG reactions suggest intestinal hyperpermeability. Removing offending foods may reduce inflammation.

Stool test

- Assessment of GI microbial status and GI function. GI imbalances have been identified as involved in the pathogenesis of food sensitivities, food allergies, and autoimmune disorders.

CBC w/diff, CMP-14, and Iron Panel

Micronutrient Deficiencies for IBD

Pain

Tissue damage

TABLE 15.1
Malnutrition in Inflammatory Bowel Disease

Deficiency	Crohn's Disease	Ulcerative Colitis	Treatment
Negative nitrogen balance	69%	Unknown	Adequate energy and protein
Vitamin B12	48%	5%	1000 mcg/day × seven days, then monthly
Folate	67%	30–40%	1 mg/day
Vitamin A	11%	Unknown	5000–25,000 IU/day
Vitamin D	75%	35%	5000–25,000 IU/day
Calcium	13%	Unknown	1000–1200 mg/day
Potassium	5–20%	Unknown	Variable
Iron	39%	81%	Iron Gluconate 300 mg TID
Zinc	50%	Unknown	Zn Sulfate 220 mg qd or BID

Kohlsstadt, I. 2013

Micronutrient deficiencies in inflammatory bowel disease

Roni Weisshof and Irit Chermesh

Purpose of review
Malnutrition, protein-energy, and micronutrient deficiencies are common among patients with inflammatory bowel disease (IBD). The deficiencies are a manifestation of the complicated disease and a cause of morbidity. The present review summarizes recent advances and evidence-based knowledge regarding micronutrients in relation to patients with IBD.

Recent findings
Micronutrient deficiencies occur in more than half of patients with IBD. Most common are deficiencies of iron, B12, vitamin D, vitamin K, folic acid, selenium, zinc, vitamin B6, and vitamin B1. Deficiencies are more common in Crohn's disease than in ulcerative colitis, and more in active disease than at times of remission. Micronutrient deficiency is associated with prolonged and complicated course of disease. Iron deficiency is the most common cause for anemia. Definite diagnosis of B12 deficiency cannot be established by serum levels alone. Vitamin D and vitamin K deficiencies are thought to be associated with heightened inflammatory state. The relationship of these deficiencies with bone disease is controversial. The present review focuses on the significance, epidemiology, treatment options, and recommendations regarding micronutrient deficiencies in IBD.

Summary
Micronutrient deficiencies are common and have clinical significance. High suspicion for micronutrient deficiencies is advocated so that treatable causes of morbidity are treated appropriately and late and irreversible sequlae are prevented.

Keywords
inflammatory bowel disease, malnutrition, micronutrients

KEY POINTS

- Iron, B12, vitamin D, vitamin K, folic acid, selenium, zinc, vitamin B6, and vitamin B1 deficiencies are common in patients with IBD.
- Iron deficiency is the leading cause of anemia in patients with IBD, and usually correlates with disease activity. The threshold for treatment, route (parenteral or oral), and dosage depend on level of deficiency, symptomatology, level of hemoglobin, and disease activity.
- Vitamin K and vitamin D deficiencies correlate with disease activity. Their role in metabolic bone disease is questionable. There is evidence regarding their role in inflammation.
- Definite diagnosis of vitamin B12 deficiency necessitates functional studies such as low homocysteine or high methylmalonilic acid levels. The only risk factor for B12 deficiency is ileal resection of more than 30 cm; otherwise, the prevalence of deficiency is equivalent to that of the general population.

. Curr Opin Clin Nutr Metab Care. 2015 Nov;18(6):576-81

Curr Opin Clin Nutr Metab Care. 2015 Nov;18(6):576-81

IBS vs IBD

IBS

- Visceral hypersensitivity
- Brain-gut axis
- 3 mo with onset in previous 6 mo
- Increased IP
- Gas
- Abdominal pain/cramping
- Constipation
- Diarrhea
- Can overlap with SIBO

IBD

- Chronic Inflammation
- Tissue damage
- Malnutrition
- Bone loss
- Anemia
- Nutrient deficiencies
- Genetic susceptibility
- Environmental and autoimmune triggers

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Case Series

Meet Lori

- 46 y/o Caucasian female
- 164 lbs 6 oz, Ht: 66 inches BMI: 26.53
- BP: 122/74
- PMH: DM II (failed metformin due to GI side effects), ADD, headaches, anxiety, HTN, HLD, UTI's and depression; Hx idiopathic pancreatitis 2018
- Surgical Hx: 1990: C- section, 1996: C-section, 1998, 1999,2002,2005: adhesion removal, 2001: gallbladder removal; 2005: hysterectomy, 2009: hip repair, 2012: hernia repair, 2015: tummy tuck and bladder sling for rectocele 11/2018;
- Allergies: Bactrim- hives or rash
- Social Hx: Mother to two children, lives with son and husband,

Current Med list

Prescription medications:

- Adderall 20 mg by mouth twice a day
- Ativan 0.5 Mg by mouth daily
- Lexapro 10 Mg by mouth daily
- Lisinopril 10 Mg by mouth daily
- Simvastatin 40 Mg by mouth daily at bedtime
- Trulicity 4.5 mg subQ weekly

Over-the- Counter

- Berberine 500mg twice daily
- Cyanocobalamin (vit B-12) 1,000 mcg under tongue daily
- Magnesium citrate 100 mg tablet at bedtime
- Vitamin D3 25 mcg (1,000 unit) capsule

HPI- Pertinent Review of Symptoms

- GENERAL - denies fever, or chills
- MOUTH - unremarkable
- GASTROINTESTINAL - + constipation, + blood in stool per patient
- GENITOURINARY - +dyspareunia, significant and undergoing pelvic floor PT
- NEUROLOGICAL - denies localized numbness, weakness, or tingling
- PSYCHIATRIC - +ADD
- ENDOCRINE – blood glucose levels uncontrolled

HPI

- Constipation began years ago
  - Associated signs and symptoms are cramping and diarrhea. She has had blood in the stool, sees it mostly when stool is hard.
- UTI symptoms which began 1 week ago
  - No flank pain
  - It is relieved by taking 1 scoop a day of d-mannose.
  - She did home strips, leukocytes are + but not nitrates.

Conventional Medicine Approach for IBS

Disease	Altered Bowel habit	Abdominal pain	Bloating
IBS-D	loperamide, bile acid sequestrants, ondansetron, ramosetron, eluxadoline	antispasmodics,TCAS, eluxadoline, psychological therapy	probiotics rifaximin
IBS-C	water soluble fiber, osmotic laxatives, linaclotide lubiprostone	antispasmodics, linaclotide, SSRIs, psychological therapy	probiotics rifaximin
IBS-M	See above for symptomatic management	antispasmodics, TCAs (preferred), SSRIs, psychological therapy	probiotics rifaximin

- Approaches to IBS involve limiting exposure to potentially aggravating foods and pharmacologic management of symptoms.
- Classification of IBS into diarrhea, constipation, or mixed symptoms determines drug therapy.
- Trial of a FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet is recommended first with gradual reintroduction of foods to determine triggers.

Altered from: Barbara et al. An expert consensus–based proposed treatment algorithm for PI-IBS. Gastroenterology.https://www.gastrojournal.org/article/S0016-5085(18)34766-8/fulltext
Published July 15 2018. Accessed October 18 2021.

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IBS Treatment

- Diet diary- identify specific foods that exacerbate symptoms
- Dietary restriction of gluten improves symptoms in many with IBS
- Fructose and sorbitol can exacerbate symptoms in those with visceral hypersensitivity
- Caffeine or high fat diet can stimulate colonic motility
- Carbohydrate malabsorption can also exacerbate IBS symptoms
- Identify medications and/or supplements that may be contributing to their symptoms

Support motility and elimination

Magnesium citrate

- Soluble organic salt form of magnesium that helps promote bowel relaxation
- Helps ease constipation by increasing fluid in the small intestine (makes stools softer)
- ~300 – 600 mg/d

Triphala

- Consists of three fruits: Amalaki, Bibhitaki, and Haritaki.
- Haritaki has the strongest laxative powers of these three fruits.
- Bibhitaki has both laxative and astringent properties.
- ~ 1 gram/d

Aloe vera

- In a animal model of irritable bowel syndrome (IBS), aloe vera used in combination with German chamomile (Matricaria recutita) was effective at reducing TNF-α, lipid peroxidation and myeloperoxidase activity, and also delayed gastric emptying and bowel transit time, suggesting that aloe could be a useful adjunct for diarrhea-dominant IBS (IBS-D).
  - *Asadi-Shahmirzadi A, Mozaffari S, Sanei Y, Baeeri M, Hajiaghaee R, Monsef-Esfahani HR, Abdollahi, M. Benefit of Aloe vera and Matricaria recutita mixture in rat irritable bowel syndrome: Combination of antioxidant and spasmolytic effects. Chin J Integr Med. 2012 Dec 21.*

Fiber

- Avoid Fructooligosaccharides (FOS) and inulin

Probiotics

Use multispecies probiotics

Use once symptoms have resolved (gas, bloating, motility issues)

- If used too soon, can make symptoms worse
- Avoid probiotics containing prebiotics as this can exacerbate symptoms

Saccharomyces cerevisiae CNCM I-3856

- This is a specific patented probiotic strain that has been shown to help improve gastrointestinal comfort and intestinal flora. Clinical trials have demonstrated that this strain survives transit through the gastrointestinal tract, has anti-inflammatory properties and reduces the perception of intestinal pain. It has been shown to reduce digestive discomfort after four weeks of consumption.

S. boulardii has been tested for clinical efficacy in several types of acute gastrointestinal conditions, including antibiotic-associated diarrhea, *Clostridium difficile* infection, acute diarrhea, traveler's diarrhea, Crohn's disease, Ulcerative Colitis, IBS, and *H. pylori* infections.

NCP Nutrition in Clinical Practice | aspen LEADING THE SCIENCE AND PRACTICE OF CLINICAL NUTRITION

Clinical Research

Low-FODMAP Diet Is Associated With Improved Quality of Life in IBS Patients—A Prospective Observational Study

Tim L. Kortlever MSc, Sebastiaan Ten Bokkel Huinink BSc, Marleen Offereins MSc, Clarice Hebblethwaite BSc (Hons), NZRD, Leigh O'Brien BSc, PGDip Diet, NZRD ... See all authors

First published: 15 January 2019 | https://doi.org/10.1002/ncp.10233 | Citations: 4

Background

The low fermentable oligosaccharide, disaccharide, monosaccharide, and polyol (FODMAP) diet is effectively manages irritable bowel syndrome (IBS) symptoms. Long-term low-FODMAP studies rarely report quality of life (QoL). We aimed to determine the effect of low-FODMAP diet on long-term QoL, gastrointestinal (GI) and non-GI symptoms in IBS patients.

Methods

A prospective observational study of IBS patients referred for low-FODMAP dietary advice was performed. The primary outcome of QoL and secondary outcomes of GI symptoms, anxiety/depression, fatigue, sleep quality, and happiness were obtained at baseline, 6 weeks (T6), and 6 months (T26).

Results

111 patients were recruited. 91.0%, 71.6%, and 50.5% of participants completed baseline, T6, and T26 assessments, respectively. There were significant improvements in QoL from baseline at T6 and T26 (both $P < 0.001$). Significant reductions were seen in GI symptoms at T6 and T26 (both $P < 0.001$), fatigue at T6 and T26 (both $P < 0.003$), and anxiety at T6 and T26 (both $P < 0.007$), compared with baseline. A significant reduction was seen for depression ($P < 0.010$) from baseline at T26, and a significant increase was seen for both tality (both $P < 0.04$) from baseline at T26. There was a significant een GI symptom response and change in QoL, anxiety, depression, and 034).

Conclusion

Low-FODMAP diet was associated with improved long-term QoL and GI symptoms, reduced fatigue and anxiety/depression, and increased happiness and vitality. These data support a wider range of benefits for IBS patients consuming a low-FODMAP diet.

Treatment Considerations: 4 vs 5R

Remove	• Food sensitivities, alcohol, aspirin, NSAIDS from the diet. • Use antimicrobials for dysbiosis, infection, and/or parasites.
Replace	• Digestive support to improved nutrient absorption and metabolism • May include digestive enzymes, or agents that promote improved motility and regular bowel movements.
Reinoculate	• Provide an environment where good bacteria can thrive and where bad ones cannot • Use pre- and probiotics.
Repair	• Support of the cellular repair process by providing specific nutritional support for the regeneration of the GI protective barrier • GI mucosa with healing nutrients and botanicals
Rebalance	• Lifestyle factors that influence the gut bacteria such as stress, sleep, exercise and relationships and assure ongoing gut health.

Serum-Derived Bovine Immunoglobulin (SBI IGG)

- Medical Food formula (EnteraGam®) is formulated as a powder that is mixed with liquids of food to prevent diarrhea associated with IBS-D

- It works by binding antigens on bacteria, fungi, or toxic substances and preventing them from leaking through tight junctions between cells in the GI tract causing inflammation

EnteraGam® [product information]. Ankeny, IA: Entera Health, Inc.; October 2020.
Wilson D, et al. Clin Med Insights Gastroenterol. 2013;6:CGast.S13200. https://doi.org/10.4137/CGast.S13200. doi: 10.4137/CGast.S13200.

SBI IGG

Restores homeostasis of the gut barrier

Intestinal barrier function

- Improving gut permeability
- Preventing antigenic translocation across tight junctions

Nutrient absorption

- IgG normalizes gut bacteria improving nutrient utilization

Impact on immune balance (IgG)

- Activates complement (serum system that can destroy
- viruses and bacteria to protect from infection)
- Protects tissues
  - Allows direct binding to microbial cells and interferes with
  - their ability to enter or damage the intestinal cells
  - ↓ intestinal mucosal damage
  - ↓ inflammatory cell infiltration
  - ↓ expression of inflammatory cytokines

EnteraGam® [product information]. Ankeny, IA: Entera Health, Inc.; October 2020.
Wilson D, et al. Clin Med Insights Gastroenterol. 2013;6:CGast.S13200.
https://doi.org/10.4137/CGast.S13200. doi: 10.4137/CGast.S13200.

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DOI: 10.3748/wjg.v21.i11.3361

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CASE REPORT

New therapeutic option for irritable bowel syndrome: Serum-derived bovine immunoglobulin

Larry Good, Roxanne Rosario, Raymond Panas

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Raymond Panas, Department of Medical Affairs, Entera Health, Inc., Cary, NC 27518, United States
Author contributions: Good L and Rosario R had full access to review and pull available data from the medical records; Good L and Panas R consolidated and analyzed the collected data; Good L, Rosario R, and Panas R contributed to the organization and writing of the manuscript.

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well as other symptoms (*i.e.*, abdominal pain and urgency) in patients with irritable bowel with diarrhea (IBS-D) and human immuno virus-associated enteropathy. This case serie the outcomes of 14 IBS patients who received SB addition to standard of care at an individual ph clinical practice. The patients: 2 IBS with co (IBS-C), 7 IBS-D, 2 mixed diarrhea and consti (IBS-M) and 3 undefined IBS (IBS-U; also de some physicians as IBS-Bloating), ranged in 22-87 years. SBI (5 g or 10 g daily dose) v to the patient's current standard care and fo several weeks to determine if symptoms were with the addition of SBI. Overall, 12 of the 1 indicated some level of improvement throu questioning of the patients regarding change prior visit. One IBS-Bloating patient had a res symptoms and two patients (1 IBS-Bloating and discontinued therapy because of insufficient relief. The 12 patients who continued on therapy reported an overall improvement in symptoms with better stool consistency,

The mechanism of action of SBI is postulated to involve binding to microbial components, maintaining immune balance in the gastrointestinal tract, managing gut barrier function including increasing expression of the tight junction proteins zonala occludens-1 (ZO1) and occludin, and improving nutrient uptake[18]. As such, SBI may provide distinct nutrition in the form of immunoglobulins and other proteins for patients and physicians when conventional therapies fail to adequately manage IBS-D.

Oral serum-derived bovine immunoglobulin/ protein isolate (SBI) has been shown in clinical studies to reduce loose stools and improve stool consistency as well as other symptoms (i.e. abdominal pain, bloating, and urgency) in patients with irritable bowel syndrome with diarrhea (IBS-D) and HIV associated enteropathy.

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Clinical Medicine Insights: Gastroenterology

Evaluation of Serum-Derived Bovine Immunoglobulin Protein Isolate in Subjects with Diarrhea-Predominant Irritable Bowel Syndrome

Dale Wilson[1], Malkanthi Evans[2], Eric Weaver[3], Audrey L. Shaw[3] and Gerald L. Klein[3]

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ABSTRACT

BACKGROUND: There is increased interest in combining nutritional modalities with pharmacological therapies for managing patients with diarrhea-predominant IBS (IBS-D).

AIM: A randomized, double-blind, placebo-controlled study to evaluate the impact of oral serum-derived bovine immunoglobulin/protein isolate (SBI) on gastrointestinal symptom scores and quality of life (QoL) in subjects with IBS-D.

METHODS: Study subjects previously diagnosed with IBS-D according to ROME II criteria were recruited from London, Ontario, Canada and assigned to receive 5 g/day SBI, 10 g/day SBI, or placebo for 6 weeks. Daily symptom frequency and severity scores and a modified IBS-36 questionnaire assessed the impact of nutritional intervention. Laboratory assessments were performed at screening and end of treatment (EOT) to evaluate safety. Within-group comparisons of changes in number of days per week with symptoms and symptom severity were conducted on the per-protocol population of subjects using a t-test.

RESULTS: Subjects who received SBI at 10 g/day ($N = 15$) had statistically significant within-group reductions in abdominal pain ($p < 0.01$), loose stools ($p < 0.01$), bloating ($p < 0.05$), flatulence ($p < 0.01$), urgency ($p < 0.05$) and any symptom ($p < 0.01$) at EOT vs. baseline. Subjects receiving 5 g/day of SBI ($N = 15$) realized statistically significant within-group reductions in days with flatulence ($p < 0.035$), incomplete evacuation ($p < 0.05$), and any symptom ($p < 0.01$). There were no significant changes in QoL scores or in hematology or clinical chemistry among treatment groups.

CONCLUSIONS: This pilot study showed that nutritional therapy with either 10 g/day or 5 g/day of SBI in 30 patients was well tolerated and resulted in statistically significant within group improvements in both symptom days and in daily symptom scores in subjects with IBS-D. Additional studies are underway with larger numbers of subjects to validate these findings.

KEYWORDS: irritable bowel syndrome, bovine serum immunoglobulin, diarrhea-predominant

10 grams/day improved abdominal pain, loose stools, bloating, flatulence, urgency, and any symptom vs. baseline in patients with IBS-D

1. Wilson D et al Clin Med Insights Gastroenterol. 2013;6:CGast.S13200. https://doi.org/10.4137/CGast.S13200.

JPEN Journal of Parenteral and Enteral Nutrition | aspen LEADING THE SCIENCE AND PRACTICE OF CLINICAL NUTRITION

Brief Communication

Glutamine Restores Tight Junction Protein Claudin-1 Expression in Colonic Mucosa of Patients With Diarrhea-Predominant Irritable Bowel Syndrome

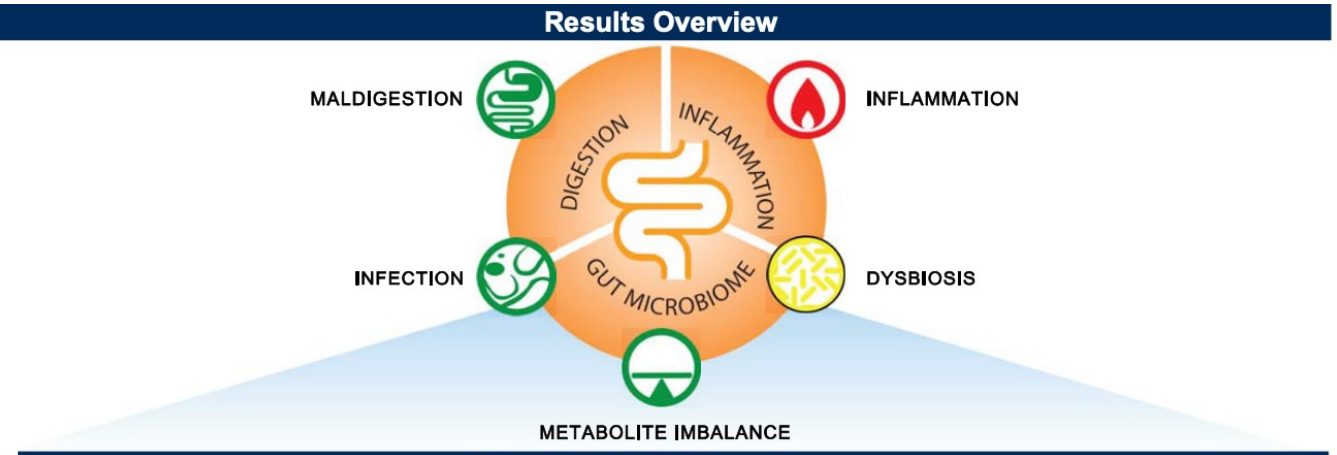
Julien Bertrand PhD, Ibtissem Ghouzali MSc, Charlène Guérin BSc, Christine Bôle-Feysot BSc Gouteux BSc, Pierre Déchelotte MD, Philippe Ducrotté MD, Moïse Coëffier PhD

First published: 13 May 2015 | https://doi.org/10.1177/0148607115587330 | Citations: 15

Cytokine concentrations in culture media were not modified by glutamine treatment. Conclusion: Glutamine increased claudin-1 expression in the colonic mucosa of patients with IBS-D. In addition, glutamine effect seems to be dependent on basal expression of tight junction proteins.

Abstract

*Background:*Recent studies showed that patients with diarrhea-predominant irritable bowel syndrome (IBS-D) had an increased intestinal permeability as well as a decreased expression of tight junctions. Glutamine, the major substrate of rapidly dividing cells, is able to modulate intestinal permeability and tight junction expression in other diseases. We aimed to evaluate, ex vivo, glutamine effects on tight junction proteins, claudin-1 and occludin, in the colonic mucosa of patients with IBS-D. *Materials and Methods:* Twelve patients with IBS-D, diagnosed with the Rome III criteria, were included (8 women/4 men, aged 40.7 ± 6.9 years). Colonic biopsy specimens were collected and immediately incubated for 18 hours in culture media with increasing concentrations of glutamine from 0.6–10 mmol/L. Claudin-1 and occludin expression was then measured by immunoblot, and concentrations of cytokines were assessed by multiplex technology. Claudin-1 expression was affected by glutamine ($P < .05$, analysis of variance). In particularly, 10 mmol/L glutamine increased claudin-1 expression compared with 0.6 mmol/L glutamine (0.47 ± 0.04 vs 0.33 ± 0.03, $P < .05$). In contrast, occludin expression was not significantly modified by glutamine. Interestingly, glutamine effect was negatively correlated to claudin-1 (Pearson $r = -0.83$, $P < .001$) or occludin basal expression (Pearson $r = -0.84$, $P < .001$), suggesting that glutamine had more marked effects when tight junction protein expression was altered. Cytokine concentrations in culture media were not modified by glutamine treatment. *Conclusion:* Glutamine increased claudin-1 expression in the colonic mucosa of patients with IBS-D. In addition, glutamine effect seems to be dependent on basal expression of tight junction proteins.

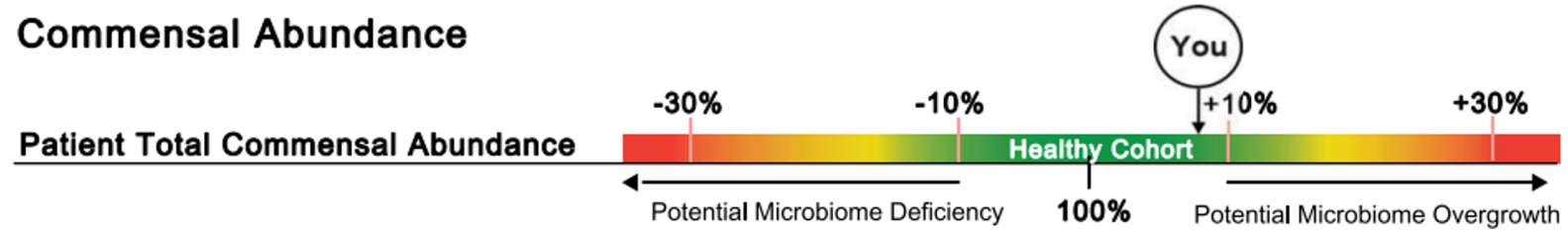


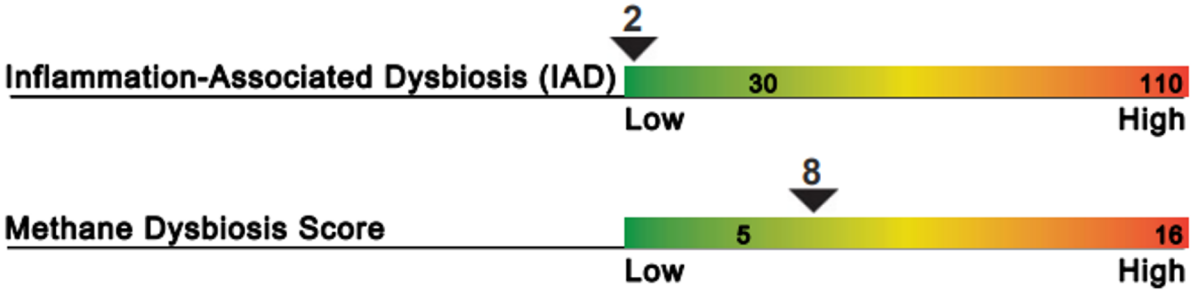
Functional Imbalance Scores

Key: < 2 : Low Need for Support | 2-3 : Optional Need for Support | 4-6 : Moderate Need for Support | 7-10 : High Need for Support

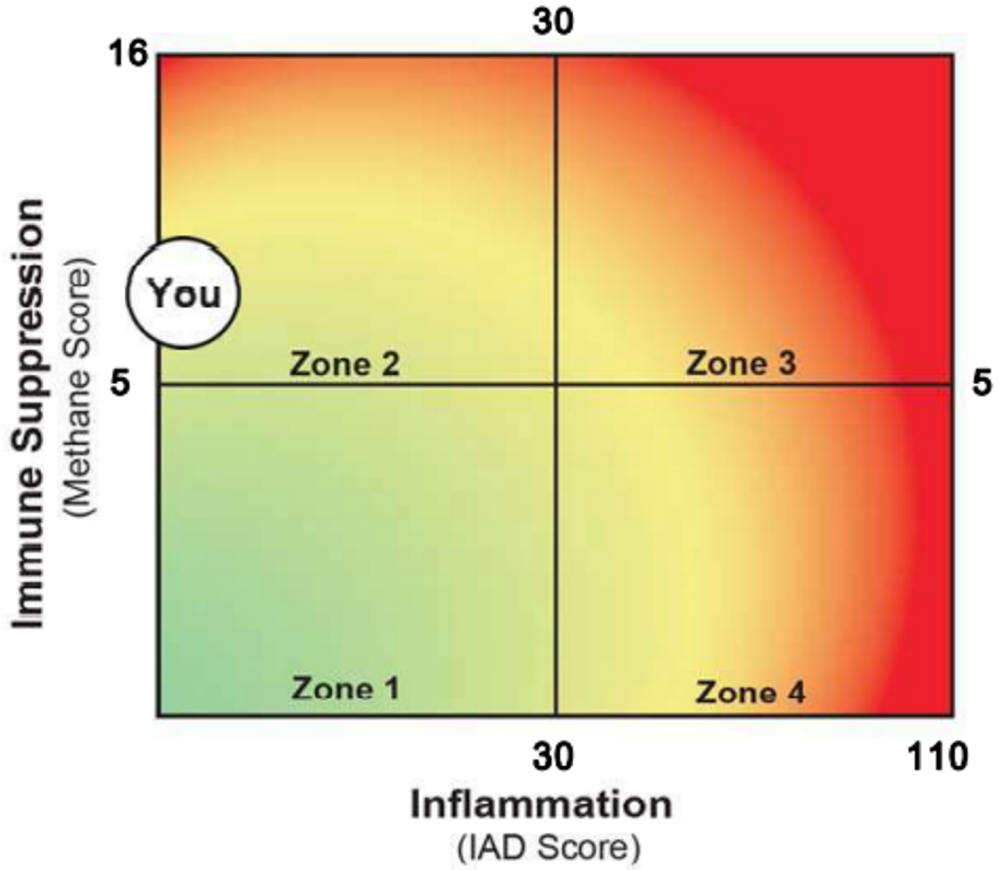
	Need for Digestive Support	Need for Inflammation Modulation	Need for Microbiome Support	Need for Prebiotic Support	Need for Antimicrobial Support
	MALDIGESTION	INFLAMMATION	DYSBIOSIS	METABOLIC IMBALANCE	INFECTION
	1	8	6	1	0
Biomarkers	Products of Protein Breakdown △ Pancreatic Elastase ● Fecal Fats ●	Calprotectin △ Eosinophil Protein X △ Secretory IgA △ Occult Blood ●	IAD/Methane Score △ Reference Variance △ PP Bacteria/Yeast ● Total Abundance ●	Beta-glucuronidase ▽ Total SCFA's ● n-Butyrate Conc. ● SCFA (%) ●	Parasitic Infection ● Pathogenic Bacteria ● PP Bacteria/Yeast ● Total Abundance ●
Therapeutic Support Options	• Digestive Enzymes • Betaine HCl • Bile Salts • Apple Cider Vinegar • Mindful Eating Habits • Digestive Bitters	• Elimination Diet/ Food Sensitivity Testing • Mucosa Support: Slippery Elm, Althea, Aloe, DGL, etc. • Zinc Carnosine • L-Glutamine • Quercetin • Turmeric • Omega-3's • GI Referral (If Calpro is Elevated)	• Pre-/Probiotics • Increase Dietary Fiber Intake • Consider SIBO Testing • Increase Resistant Starches • Increase Fermented Foods • Meal Timing	• Pre-/Probiotics • Increased Dietary Fiber Intake • Increase Resistant Starches • Increase Fermented Foods • Calcium D-Glucarate (for high beta-glucuronidase)	• Antibiotics (if warranted) • Antimicrobial Herbal Therapy • Antiparasitic Herbal Therapy (if warranted) • *Saccharomyces boulardii*

Comprehensive Stool Testing Results





Zone 2: This pattern of bacteria is associated with impaired intestinal barrier function (low fecal sIgA and EPX). Patients in this zone have higher rates of opportunistic infections (e.g. *Blastocystis spp.* & *Dientamoeba fragilis*) as well as fecal fat malabsorption. Commensal abundance is higher in this group suggesting potential bacterial overgrowth.



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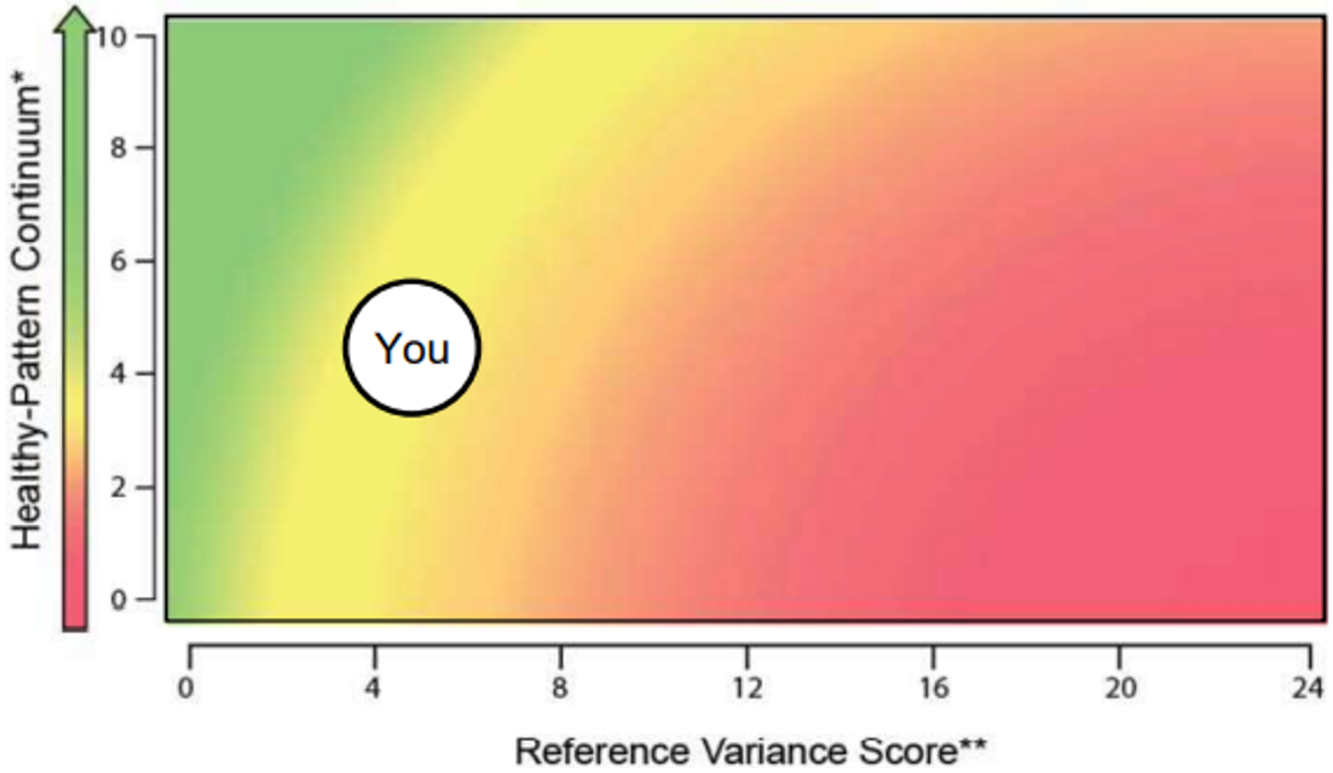
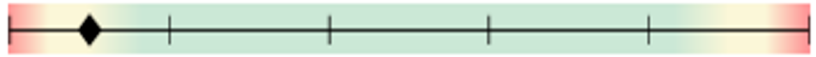
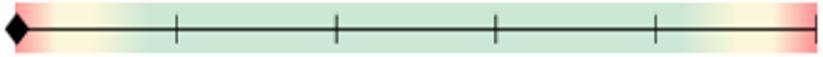
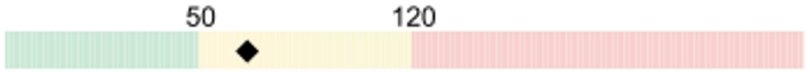


	-50% / -25% / Healthy Cohort / +25%	
Bacteroidetes Phylum		Increase in *Bacteroides* spp. and *Odoribacter* spp. seen in animal-based diets; *Prevotella* increased with plant-based diet
Firmicutes Phylum		Contains many butyrate-producers; most species responsive to plant-based diets; *Faecalibacterium* spp. is anti-inflammatory
Actinobacteria Phylum		*Bifidobacterium* is increased with plant-based diets; *Collinsella* may be proinflammatory, and is elevated with a Western-diet
Proteobacteria Phylum		Some species may be proinflammatory; *E. coli* consumes simple sugars and is lower in individuals on plant-based diets
Euryarchaeota Phylum***		*Methanobrevibacter smithii* is associated with methane production and with diets high in carbohydrates
Fusobacteria Phylum		Certain *Fusobacterium* spp. may be proinflammatory and increased on low fiber, high fat diets
Verrucomicrobia Phylum		*Akkermansia* spp. is involved in gut membrane integrity and may be increased with polyphenols and prebiotics

Digestion and Absorption

Pancreatic Elastase 1 †	334		>200 mcg/g
Products of Protein Breakdown (Total*) (Valerate, Isobutyrate, Isovalerate)	7.6		1.8-9.9 micromol/g
Fecal Fat (Total*)	13.8		3.2-38.6 mg/g
Triglycerides	<DL L		0.3-2.8 mg/g
Long-Chain Fatty Acids	12.9		1.2-29.1 mg/g
Cholesterol	0.9		0.4-4.8 mg/g
Phospholipids	<DL L		0.2-6.9 mg/g

Inflammation and Immunology

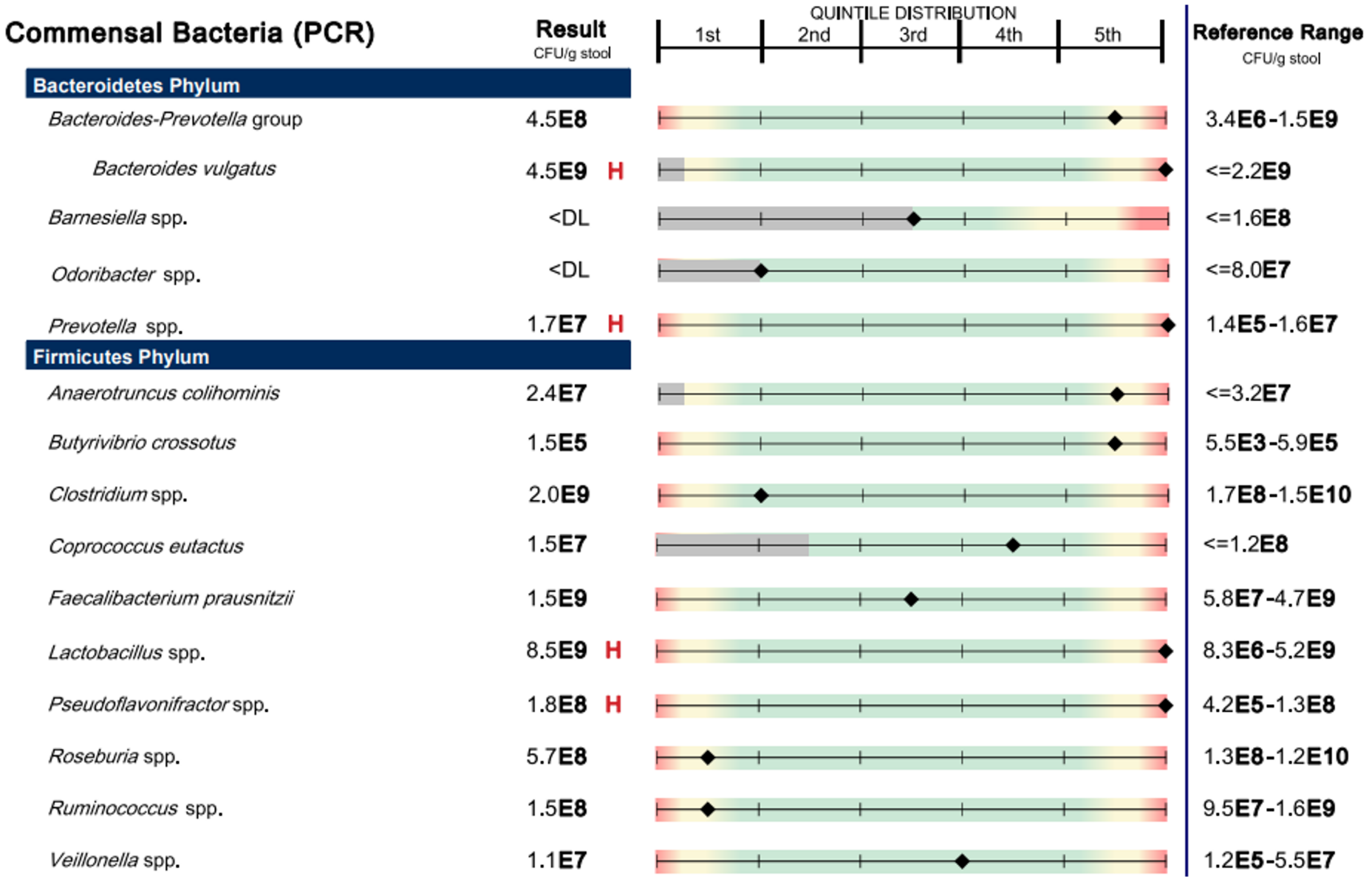
Calprotectin †	66 H		<=50 mcg/g
Eosinophil Protein X (EPX)†	2.7		<=4.6 mcg/g
Fecal secretory IgA	1,052		<=2,040 mcg/mL

Gut Microbiome Metabolites

Metabolic

Short-Chain Fatty Acids (SCFA) (Total*) (Acetate, n-Butyrate, Propionate)	44.6		>=23.3 micromol/g
n-Butyrate Concentration	8.9		>=3.6 micromol/g
n-Butyrate %	20.0		11.8-33.3 %
Acetate %	52.8		48.1-69.2 %
Propionate %	27.3		<=29.3 %
Beta-glucuronidase	393		368-6,266 U/g

Commensal Bacteria (PCR)

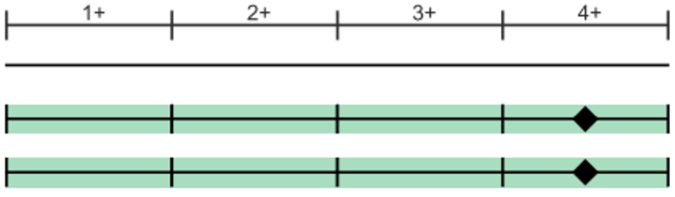


Actinobacteria Phylum			
Bifidobacterium spp.	8.1**E8**		<=6.4**E9**
Bifidobacterium longum	2.4**E7**		<=7.2**E8**
Collinsella aerofaciens	1.2**E9**		1.4**E7**-1.9**E9**
Proteobacteria Phylum			
Desulfovibrio piger	2.0**E7**	H	<=1.8**E7**
Escherichia coli	9.3**E6**		9.0**E4**-4.6**E7**
Oxalobacter formigenes	4.0**E6**		<=1.5**E7**
Euryarchaeota Phylum			
Methanobrevibacter smithii	1.9**E7**		<=8.6**E7**
Fusobacteria Phylum			
Fusobacterium spp.	5.0**E4**		<=2.4**E5**
Verrucomicrobia Phylum			
Akkermansia muciniphila	1.8**E7**		>=1.2**E6**
Firmicutes/Bacteroidetes Ratio			
Firmicutes/Bacteroidetes (F/B Ratio)	29		12-620

Microbiology Legend

NG	NP	PP	P
No Growth	Non-Pathogen	Potential Pathogen	Pathogen

Bacteriology (Culture)



Lactobacillus spp.		NG
Escherichia coli	4+	NP
Bifidobacterium	4+	NP

Additional Bacteria

alpha haemolytic Streptococcus	4+	NP
Enterococcus faecalis	4+	NP

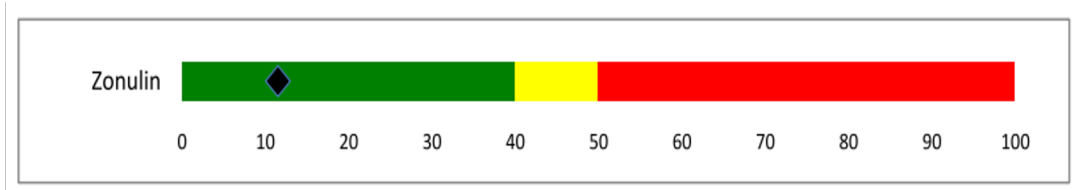
Mycology (Culture)

NG

Organism	Result	Units		Expected Result
Blastocystis spp.	<2.14e2	femtograms/microliter C&S stool	Not Detected	Not Detected
Cryptosporidium parvum/hominis	<1.76e2	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	<1.84e2	genome copies/microliter C&S stool	Not Detected	Not Detected
Entamoeba histolytica	<9.64e1	genome copies/microliter C&S stool	Not Detected	Not Detected
Giardia	<1.36e1	genome copies/microliter C&S stool	Not Detected	Not Detected

Food Intolerance Testing

List of Restricted Foods:	
4+ Reactions:	Polysorbate 80 Celery Coffee
3+ Reactions:	Cherry Cauliflower Lamb
2+ Reactions:	Apple Blueberry Cinnamon Hops Swordfish Yeast, Baker's



Zonulin	11.5 ng/ml	Normal

Other Labs

- Vitamin B12 >2000 mcg (range 232-1245)
- Folate 9.2 ng/ml (range >3)
- Vitamin B6 4.1 ug/L. (range 2.0-32.8)
- Vitamin D 47.5 ng/ml (30-100.0)
- Co-enzyme Q10 0.72 ug/ml (range 0.37-2.20)
- Copper 126 ug/dL (80-158)
- Zinc 94 ug/Dl (44-115)
- Magnesium RBC 6.0 mg/dl (range 4.2-6.8)

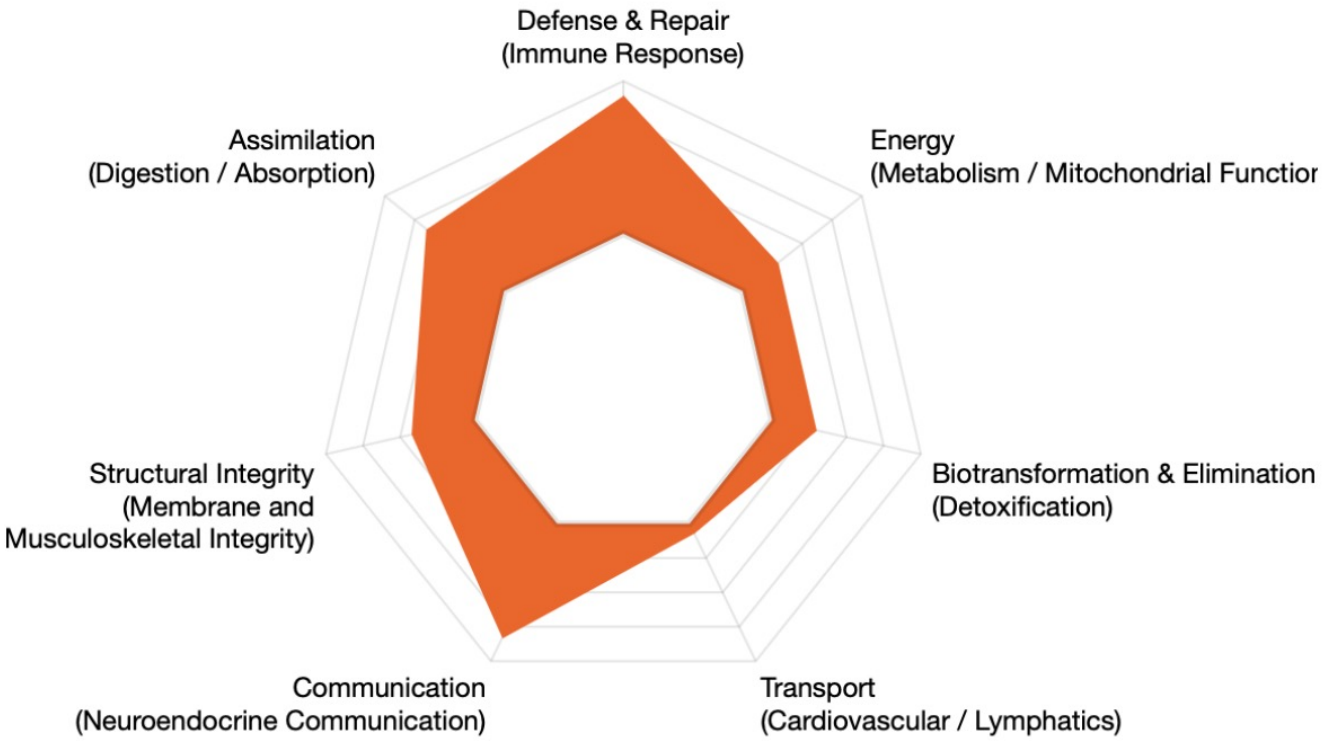
Break-Out Time

1. What labs are out of range for Lori?
    1. Any labs in range, but sub-optimal?
    2. What replacement strategies?
2. Thinking about a 5-R protocol, what would you recommend for her?
    1. Remember 5-R Stands for..
        1. Remove
        2. Replace
        3. Reinoculate
        4. Repair
        5. Rebalance
3. What dietary changes would you like Lori to make?

Meet Carla

- 34 y/o Caucasian female
- 107 lbs, 64.5 inches, BMI 18.13
- BP: 124/78
- PMH: Ulcerative Colitis, Anxiety, Insomnia
- Surgical Hx: Wisdom teeth removal
- Allergies: Bactrim- hives or rash
- Social Hx: Mother to two children, stay at home mom, wife
- Medications/ Supplements: Ancient Nutrition SBO Probiotics Ultimate
- MSQ: 26
- Calprotectin at GI appointment 135 mcg/g
- No prescription medications.

Matrix



Imbalance

Defense & Repair (Immune Response): Cancer Fhx, Stroke Fhx, Arthritis Fhx, Autoimmune Disease Fhx, Thyroid Problems Fhx, Allergies Fhx, Crohn's disease or ulcerative colitis, Conjunctivitis, Anxiety, Irritability, Blood in stools, Diarrhea, Intolerance to all dairy products, Mucus in stools, Undigested food in stools, Winter stuffiness, Sensitive to poison ivy or oak, Pre-menstrual Decreased sleep, Pre-menstrual Irritability, Carpets or Rugs

Energy (Metabolism / Mitochondrial Function): Cancer Fhx, Stroke Fhx, Diabetes Fhx, Thyroid Problems Fhx, Diabetes during or after pregnancy, Sweet cravings, Carpets or Rugs

Biotransformation & Elimination (Detoxification): Cancer Fhx, Thyroid Problems Fhx, Irritability, Cellulite, Pre-menstrual Decreased sleep, Pre-menstrual Irritability, Carpets or Rugs, Birth Control Pills

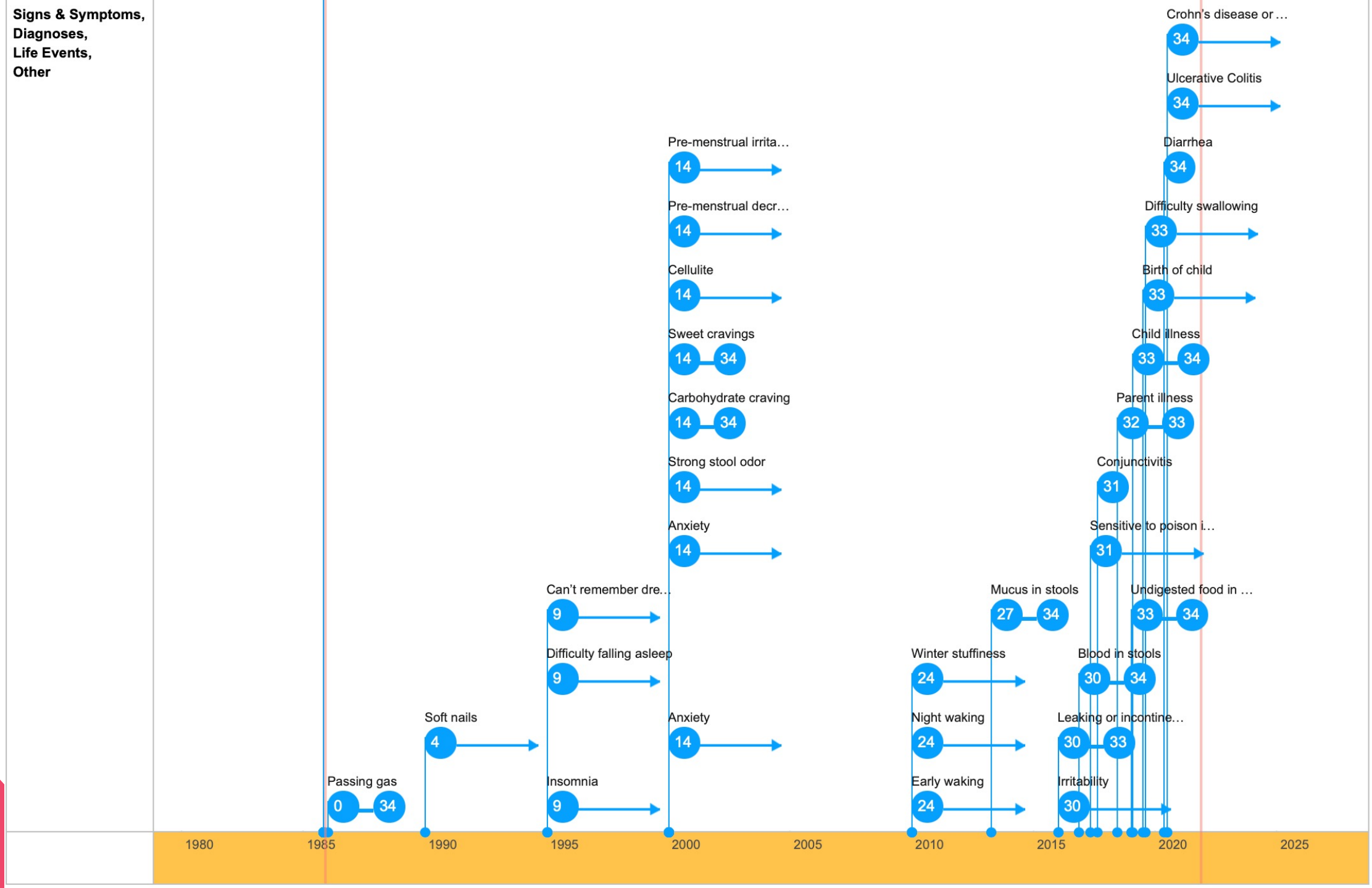
Transport (Cardiovascular / Lymphatics): Stroke Fhx, Diabetes Fhx

Communication (Neuroendocrine Communication): Cancer Fhx, Diabetes Fhx, Autoimmune Disease Fhx, Thyroid Problems Fhx, Diabetes during or after pregnancy, Breast feeding issues, Difficulty falling asleep, Early waking, Night waking, Can't remember dreams, Anxiety, Irritability, Leaking or incontinence, Carbohydrate craving, Pre-menstrual Decreased sleep, Pre-menstrual Irritability, Birth Control Pills

Structural Integrity (Membrane And Musculoskeletal Integrity): Stroke Fhx, Arthritis Fhx, Crohn's disease or ulcerative colitis, Breast feeding issues, Leaking or incontinence, Difficulty swallowing, Cellulite

Assimilation (Digestion / Absorption): Allergies Fhx, Crohn's disease or ulcerative colitis, Blood in stools, Diarrhea, Difficulty swallowing, Passing Gas, Intolerance to all dairy products, Mucus in stools, Strong stool odor, Undigested food in stools, Sweet cravings, Soft Nails

Signs & Symptoms,
Diagnoses,
Life Events,
Other



HPI

- Ulcerative Colitis: Seven years ago, she started to occasionally have mucous in the stool and stools were softer. Officially diagnosed in the last year, after a colonoscopy.
- First symptoms of increased stools and blood in stools four years ago post delivery of her first child. Increased urgency to defecate developed during 2nd pregnancy last year.
- Started to add dairy and gluten again during breastfeeding earlier this year and everything got worse. She was recommended mesalamine for symptoms but wants to try life-style modification first, so she started SCD diet and probiotics.

HPI/Pertinent Review of Systems

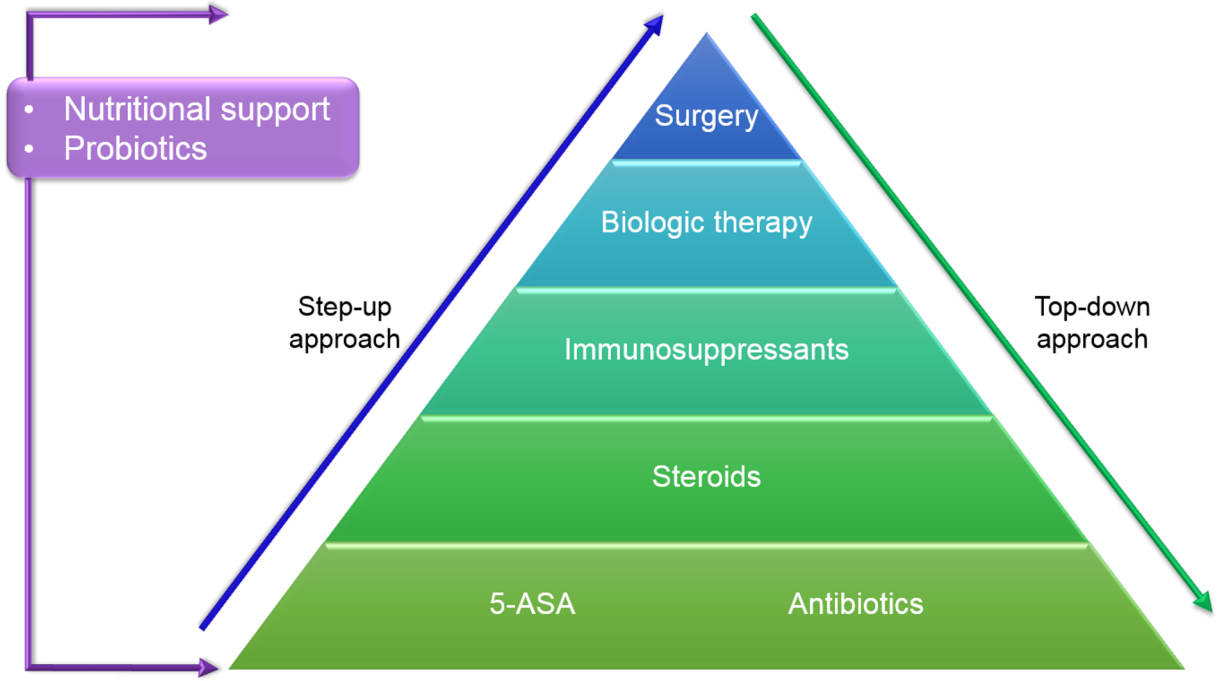
- General: Feeling well, no fever or chills
- Gastrointestinal - Ulcerative Colitis, Denies nausea and vomiting, Stools 0-3 times a day, soft but not loose most of the time. Mild abdominal pain, rated 1 on 0-10 scale. Improved since introducing probiotic and SCD diet.
- Psychiatric - Denies depression, anxiety, substance abuse, states overall becomes more anxious over certain situations. and hx of insomnia since childhood. 4-7 hours a night.
- Anxiety: States she tends to be one to have a lot of stress. She reports she doesn't have an overly stressful life. She states her life got more stressful with the birth of her first child four years ago.
- Insomnia: Stay at home Mom. Has chronically had difficulty sleeping which is also worse around her period. Difficulty turning off her mind. Has tried melatonin off and on but doesn't notice much effect. Chamomile, valerian. Saw a sleep specialist 10 years ago after a falling out with a friend. Was started on Trazodone which helped but left her feeling very groggy.

1st Visit Recommendations

- Comprehensive stool test
- Bloodwork
- Consider 5-HTP and/or Ashwagandha root before bed.

A Conventional Medicine Approach to IBD

- Treatment in IBD is usually dependent on severity at presentation.
- For mild to moderate cases, topical or oral treatments preventing inflammation in the GI tract or drugs that eliminate potential causes of inflammation such as bacterial overgrowth.
- Moderate to severe cases are treated with oral or injectable drugs designed to keep the disease in remission by suppressing immune response and corticosteroids.
- In the most severe cases, surgical resection or removal of the bowel is necessary due to total blockage or perforation of the bowel.



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2. https://gastro.org/guidelines/ibd-and-bowel-disorders/

SBI improves clinical management of IBD patients who are not fully managed on traditional therapies.

1. Shafran I, et al. *Therap Adv Gastroenterol*. 2015;8(6):331-339. doi:10.1177/1756283X15593693

Therapeutic Advances in Gastroenterology *Original Research*

Management of inflammatory bowel disease with oral serum-derived bovine immunoglobulin

Ther Adv Gastroenterol
2015, Vol. 8(6) 331–339
DOI: 10.1177/1756283X15593693

Ira Shafran, Patricia Burgunder, David Wei, Hayley E. Young, Gerald Klein and Bruce P. Burnett

Abstract

Introduction: The clinical effect of oral serum-derived bovine immunoglobulin/protein isolate (SBI) on symptom and disease management in patients with inflammatory bowel disease (IBD) is reported in this retrospective case series.

Methods: A single-center, retrospective chart review of IBD patients [$N = 45$; Crohn's disease (CD), $n = 38$ and ulcerative colitis (UC), $n = 7$] with limited to no response to traditional pharmaceutical therapies in controlling symptoms was performed after providing SBI (5 g/day) for nutritional support. Patients were contacted at least monthly to assess response to SBI for symptom management measured by a Likert scale (0 = none; 1 = minimal; 2 = moderate; 3 = significant; 4 = complete). Analysis of variance (ANOVA) was performed on response to therapy based on patient characteristics (age, gender, race) and IBD diagnosis. A multivariate ordered logistical regression model was performed to determine the odds ratio in overall disease management between week 1 and week 12. Finally, the overall group response and percent improvement to SBI was determined over 12 weeks.

Results: The odds ratio from the regression model demonstrated that IBD patients were 2.8 times more likely to report clinical improvement in symptom scores with the addition of SBI to their therapeutic regimens [95% confidence interval (CI) 1.266–6.016, $p = 0.011$]. Disease management was not significantly associated with age, gender, race or disease state. The percentage of patients reporting a response to SBI therapy at week 1 was 49% which increased to 76% after 12 weeks with the fraction of responders gaining significant symptom improvement doubling during the same time period (9% *versus* 20%). Overall, this group of IBD patients showed increased, steady response to SBI therapy between week 1 and 12 with no reported side effects.

Conclusion: These results suggest that SBI improves clinical management of IBD patients who are not fully managed on traditional therapies. SBI should be considered for the nutritional support of IBD regardless of disease activity, location, phenotype, duration, or complexity.

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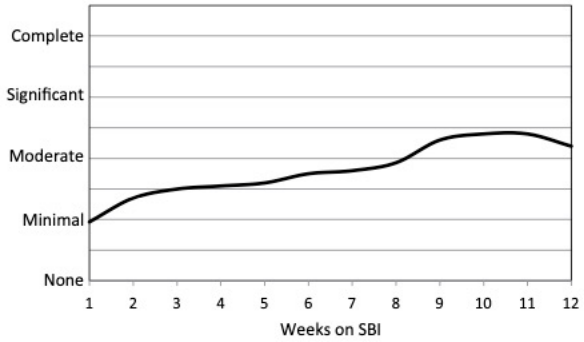

Figure 1. Average reported improved response of all inflammatory bowel disease patients ($N = 45$).

$p = 0.011$] (Table 3). This finding was significant compared with the null hypothesis corresponding to an odds ratio of 1 in which patients would have equal likelihood of reporting the same or worse disease management at 12 weeks as they did at baseline. This model also showed that response to SBI addition was not associated with age, gender, race or diagnosis.

To retrospectively capture the overall pattern of reported clinical management for the entire cohort during the time period used in the statistical analysis, average patient-reported symptom

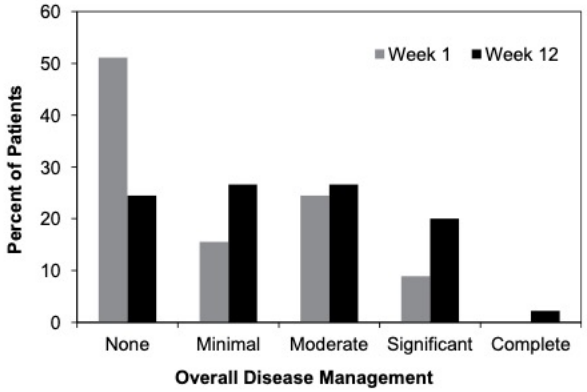

Figure 2. Per cent change in disease management at week 1 *versus* week 12.

The overall response to the addition of SBI in IBD patients suggests that the longer patients are on therapy, the better their outcomes. It is possible that addition of SBI with other therapies used concomitantly resulted in further or even synergistic benefit in these patients. Further clinical research is needed to assess SBI's effects in combination with other treatments for IBD.

Discussion

The longer they used it, the more response was reported. Needs further clinical trial to determine optimal patient populations and length of therapy.

1. Shafran I, et al. *Therap Adv Gastroenterol*. 2015;8(6):331-339. doi:10.1177/1756283X15593693

Open

Treatment of Relapsing Mild-to-Moderate Ulcerative Colitis With the Probiotic VSL#3 as Adjunctive to a Standard Pharmaceutical Treatment: A Double-Blind, Randomized, Placebo-Controlled Study

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OBJECTIVES: **VSL#3 is a high-potency probiotic mixture that has been used successfully in the treatment of pouchitis. The primary end point of the study was to assess the effects of supplementation with VSL#3 in patients affected by relapsing ulcerative colitis (UC) who are already under treatment with 5-aminosalicylic acid (ASA) and/or immunosuppressants at stable doses.**

METHODS: **A total of 144 consecutive patients were randomly treated for 8 weeks with VSL#3 at a dose of 3,600 billion CFU/day (71 patients) or with placebo (73 patients).**

RESULTS: **In all, 65 patients in the VSL#3 group and 66 patients in the placebo group completed the study. The decrease in ulcerative colitis disease activity index (UCDAI) scores of 50% or more was higher in the VSL#3 group than in the placebo group (63.1 vs. 40.8; per protocol (PP) $P=0.010$, confidence interval $(CI)_{95\%}$ 0.51–0.74; intention to treat (ITT) $P=0.031$, $CI_{95\%}$ 0.47–0.69). Significant results with VSL#3 were recorded in an improvement of three points or more in the UCDAI score (60.5% vs. 41.4%; PP $P=0.017$, $CI_{95\%}$ 0.51–0.74; ITT $P=0.046$, $CI_{95\%}$ 0.47–0.69) and in rectal bleeding (PP $P=0.014$, $CI_{95\%}$ 0.46–0.70; ITT $P=0.036$, $CI_{95\%}$ 0.41–0.65), whereas stool frequency (PP $P=0.202$, $CI_{95\%}$ 0.39–0.63; ITT $P=0.229$, $CI_{95\%}$ 0.35–0.57), physician's rate of disease activity (PP $P=0.088$, $CI_{95\%}$ 0.34–0.58; ITT $P=0.168$, $CI_{95\%}$ 0.31–0.53), and endoscopic scores (PP $P=0.086$, $CI_{95\%}$ 0.74–0.92; ITT $P=0.366$, $CI_{95\%}$ 0.66–0.86) did not show statistical differences. Remission was higher in the VSL#3 group than in the placebo group (47.7% vs. 32.4%; PP $P=0.069$, $CI_{95\%}$ 0.36–0.60; ITT $P=0.132$, $CI_{95\%}$ 0.33–0.56). Eight patients on VSL#3 (11.2%) and nine patients on placebo (12.3%) reported mild side effects.**

CONCLUSIONS: **VSL#3 supplementation is safe and able to reduce UCDAI scores in patients affected by relapsing mild-to-moderate UC who are under treatment with 5-ASA and/or immunosuppressants. Moreover, VSL#3 improves rectal bleeding and seems to reinduce remission in relapsing UC patients after 8 weeks of treatment, although these parameters do not reach statistical significance.**

Am J Gastroenterol 2010; 105:2218–2227; doi:10.1038/ajg.2010.218; published online 1 June 2010

High Dose Probiotics

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WILEY APT Alimentary Pharmacology & Therapeutics

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

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Summary

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

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

Methods: MEDLINE, EMBASE, and the Cochrane Controlled Trials Register were searched (until November 2016). Eligible randomised controlled trials (RCTs) recruited adults with UC or CD, and compared probiotics with 5-aminosalicylates (5-ASAs) or placebo. Dichotomous symptom data were pooled to obtain a relative risk (RR) of failure to achieve remission in active IBD, or RR of relapse of disease activity in quiescent IBD, with 95% confidence intervals (CIs).

Results: The search identified 12 253 citations. Twenty-two RCTs were eligible. There was no benefit of probiotics over placebo in inducing remission in active UC (RR of failure to achieve remission=0.86; 95% CI=0.68-1.08). However, when only trials of VSL#3 were considered there appeared to be a benefit (RR=0.74; 95% CI=0.63-0.87). Probiotics appeared equivalent to 5-ASAs in preventing UC relapse (RR=1.02; 95% CI=0.85-1.23). There was no benefit of probiotics in inducing remission of active CD, in preventing relapse of quiescent CD, or in preventing relapse of CD after surgically induced remission.

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

PLOS ONE

RESEARCH ARTICLE

Assessing the efficacy and safety of fecal microbiota transplantation and probiotic VSL#3 for active ulcerative colitis: A systematic review and meta-analysis

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Abstract

Background

Fecal microbiota transplantation is an effective treatment for many gastrointestinal diseases, such as *Clostridium difficile* infection and inflammatory bowel disease, especially ulcerative colitis. Changes in colonic microflora may play an important role in the pathogenesis of ulcerative colitis, and improvements in the intestinal microflora may relieve the disease. Fecal bacterial transplants and oral probiotics are becoming important ways to relieve active ulcerative colitis.

Purpose

This systematic review with meta-analysis compared the efficacy and safety of basic treatment combined with fecal microbiota transplantation or mixed probiotics therapy in relieving mild to moderate ulcerative colitis.

Methods

The PubMed, Embase, and Cochrane libraries (updated September 2019) were searched to identify randomized, placebo-controlled, or head-to-head trials assessing fecal microbiota transplantation or probiotic VSL#3 as induction therapy in active ulcerative colitis. We analyze data using the R program to obtain evidence of direct comparison and to generate intermediate variables for indirect treatment comparisons.

Results

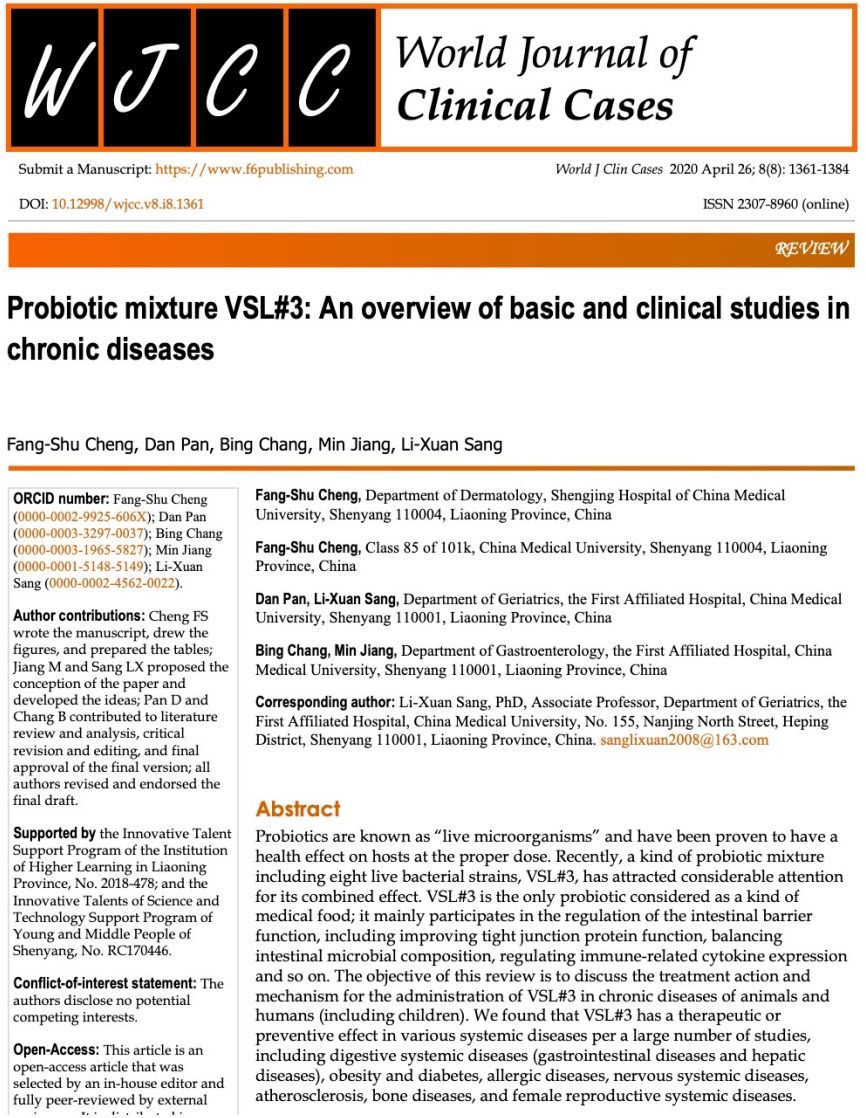
Seven randomized, double-blind, placebo-controlled trials were used as the sources of the induction data. All treatments were superior to placebo. In terms of clinical remission and clinical response to active ulcerative colitis, direct comparisons showed fecal microbiota transplantation (OR = 3.47, 95% CI = 1.93–6.25) (OR = 2.48, 95% CI = 1.18–5.21) and mixed probiotics VSL#3 (OR = 2.40, 95% CI = 1.49–3.88) (OR = 3.09, 95% CI = 1.53–6.25) to have better effects than the placebo. Indirect comparison showed fecal microbiota transplantation and probiotic VSL#3 did not reach statistical significance either in clinical remission (RR = 1.20, 95% CI = 0.70–2.06) or clinical response (RR = 0.95, 95% CI = 0.62–1.45). In terms of safety, fecal microbiota transplantation (OR = 1.15, 95% CI = 0.51–2.61) and VSL #3 (OR = 0.90, 95% CI = 0.33–2.49) showed no statistically significant increase in adverse events compared with the control group. In terms of serious adverse events, there was no statistical difference between the fecal microbiota transplantation group and the control group (OR = 1.29, 95% CI = 0.46–3.57). The probiotics VSL#3 seems more safer than fecal microbiota transplantation, because serious adverse events were not reported in the VSL#3 articles.

Conclusions

Fecal microbiota transplantation or mixed probiotics VSL#3 achieved good results in clinical remission and clinical response in active ulcerative colitis, and there was no increased risk of adverse reactions. There was no statistical difference between the therapeutic effect of fecal microbiota transplantation and that of mixed probiotics VSL#3. However, the use of fecal microbiota transplantation and probiotics still has many unresolved problems in clinical applications, and more randomized controlled trials are required to confirm its efficacy.

Good Summary of the evidence!

- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7190945/



World Journal of Clinical Cases

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DOI: 10.12998/wjcc.v8.i8.1361

ISSN 2307-8960 (online)

REVIEW

Probiotic mixture VSL#3: An overview of basic and clinical studies in chronic diseases

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Author contributions: Cheng FS wrote the manuscript, drew the figures, and prepared the tables; Jiang M and Sang LX proposed the conception of the paper and developed the ideas; Pan D and Chang B contributed to literature review and analysis, critical revision and editing, and final approval of the final version; all authors revised and endorsed the final draft.

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Abstract

Probiotics are known as "live microorganisms" and have been proven to have a health effect on hosts at the proper dose. Recently, a kind of probiotic mixture including eight live bacterial strains, VSL#3, has attracted considerable attention for its combined effect. VSL#3 is the only probiotic considered as a kind of medical food; it mainly participates in the regulation of the intestinal barrier function, including improving tight junction protein function, balancing intestinal microbial composition, regulating immune-related cytokine expression and so on. The objective of this review is to discuss the treatment action and mechanism for the administration of VSL#3 in chronic diseases of animals and humans (including children). We found that VSL#3 has a therapeutic or preventive effect in various systemic diseases per a large number of studies, including digestive systemic diseases (gastrointestinal diseases and hepatic diseases), obesity and diabetes, allergic diseases, nervous systemic diseases, atherosclerosis, bone diseases, and female reproductive systemic diseases.

Other Considerations for IBD

- Curcumin (Turmeric)[1-3]
  - It can be considered as a complement to standard therapy in active and quiescent UC.
  - Induction of remission: 3 g/daily + standard therapy
  - Maintenance of remission: 2-3 g/daily + standard therapy
- Acupuncture[3]
- Cognitive-Physical (Mind-Body) Therapies[3]
- Hypnotherapy[3]
- Exercise[3]
- Ginger[4]
  - 2,000 mg a day improved QOL and reduced oxidative stress in UC.

1. *Clin Gastroenterol Hepatol. 2006 Dec; 4(12):1502-6.*
2. *Clin Gastroenterol Hepatol. 2015 Aug; 13(8):1444-9.e1.*
3. Gastroenterol Hepatol (N Y). 2018 Jul; 14(7): 415–425.
4. Complement Ther Med. 2019 Apr;43:1-6. doi: 10.1016/j.ctim.2018.12.021.

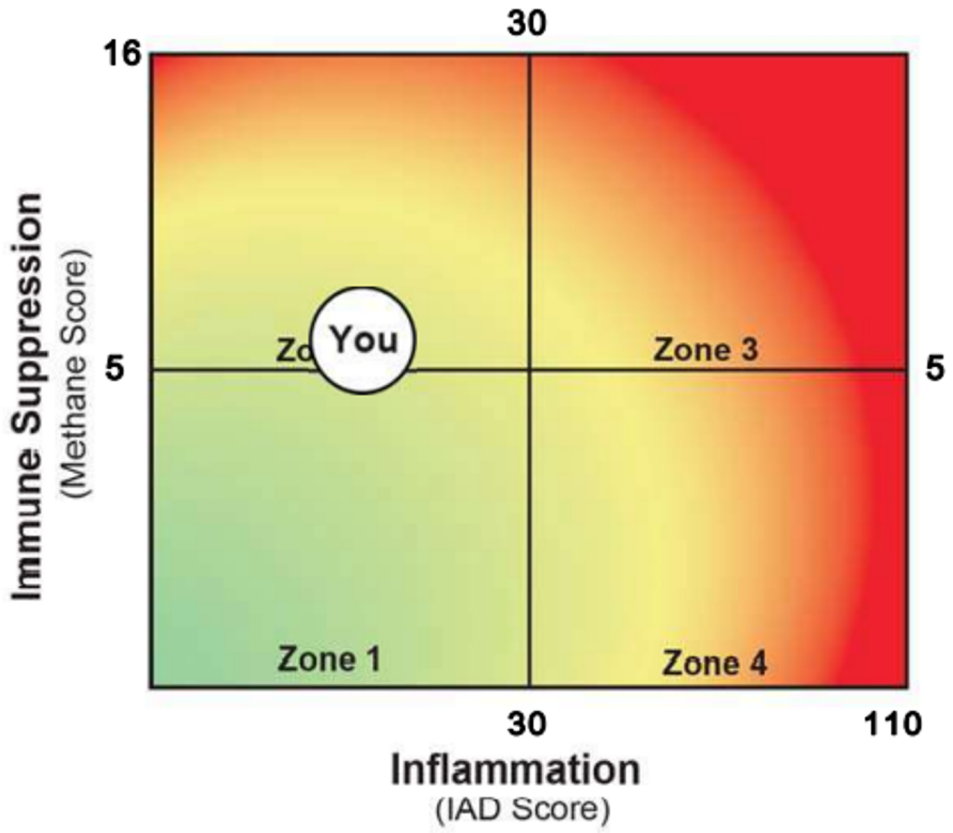
Comprehensive Stool Testing Results

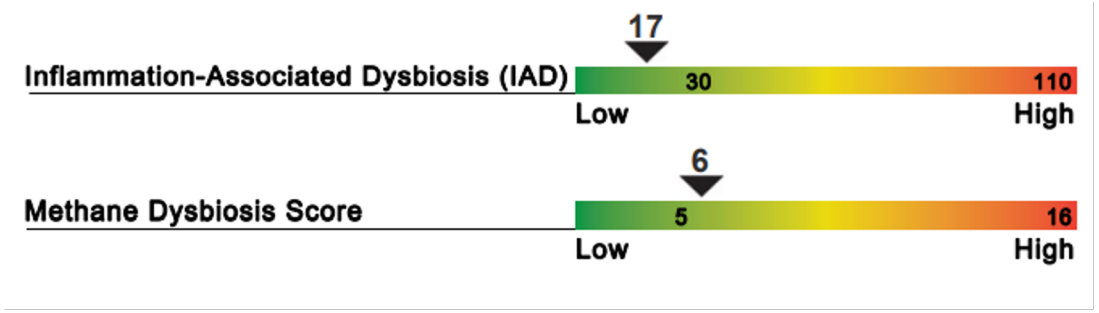
Results Overview

Functional Imbalance Scores

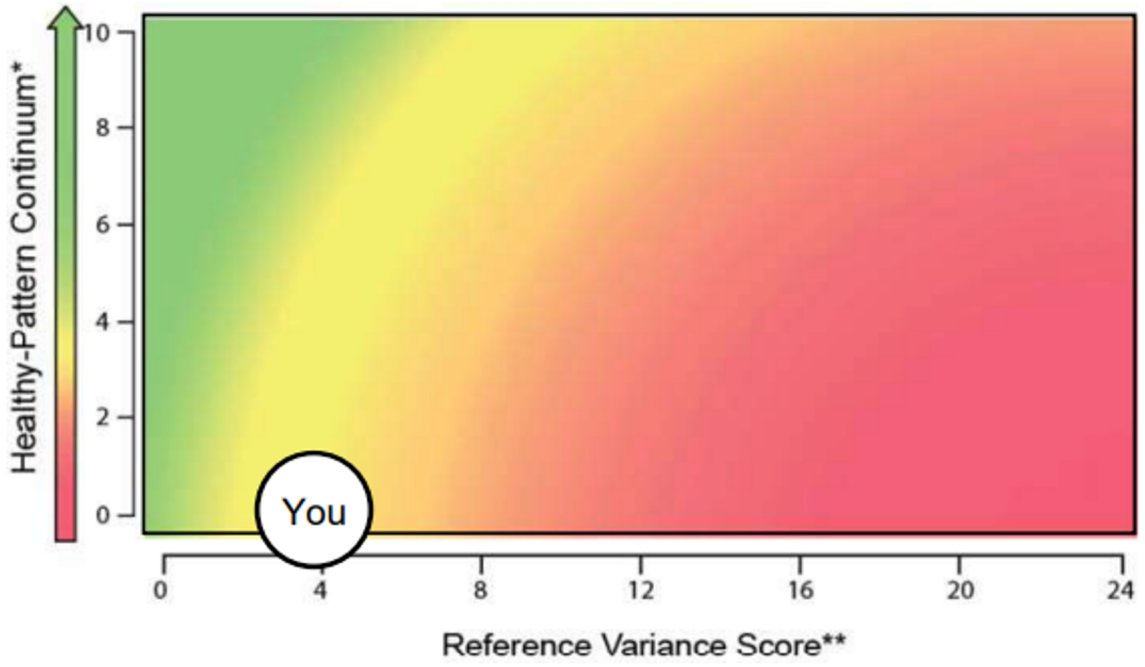
Key: < 2 : Low Need for Support; 2-3 : Optional Need for Support; 4-6 : Moderate Need for Support; 7-10 : High Need for Support

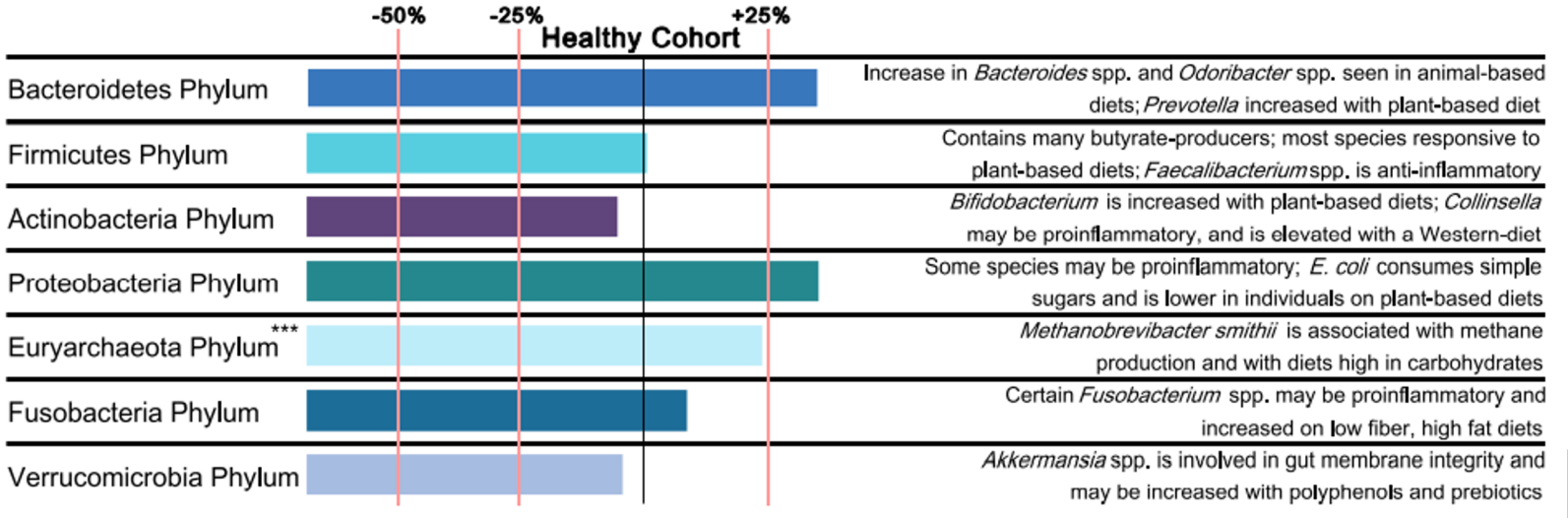
	Need for Digestive Support	Need for Inflammation Modulation	Need for Microbiome Support	Need for Prebiotic Support	Need for Antimicrobial Support
	MALDIGESTION	INFLAMMATION	DYSBIOSIS	METABOLIC IMBALANCE	INFECTION
	1	8	5	0	0
Biomarkers	Pancreatic Elastase ● Products of Protein Breakdown ● Fecal Fats ●	Calprotectin △ Eosinophil Protein X △ Secretory IgA △ Occult Blood ●	IAD/Methane Score △ Reference Variance △ Total Abundance △ PP Bacteria/Yeast ●	Total SCFA's ● n-Butyrate Conc. ● SCFA (%) ● Beta-glucuronidase ●	Total Abundance △ Parasitic Infection ● Pathogenic Bacteria ● PP Bacteria/Yeast ●
Therapeutic Support Options	• Digestive Enzymes • Betaine HCl • Bile Salts • Apple Cider Vinegar • Mindful Eating Habits • Digestive Bitters	• Elimination Diet/ Food Sensitivity Testing • Mucosa Support: Slippery Elm, Althea, Aloe, DGL, etc. • Zinc Carnosine • L-Glutamine • Quercetin • Turmeric • Omega-3's • GI Referral (If Calpro is Elevated)	• Pre-/Probiotics • Increase Dietary Fiber Intake • Consider SIBO Testing • Increase Resistant Starches • Increase Fermented Foods • Meal Timing	• Pre-/Probiotics • Increased Dietary Fiber Intake • Increase Resistant Starches • Increase Fermented Foods • Calcium D-Glucarate (for high beta-glucuronidase)	• Antibiotics (if warranted) • Antimicrobial Herbal Therapy • Antiparasitic Herbal Therapy (if warranted) • *Saccharomyces boulardii*





Zone 2: This pattern of bacteria is associated with impaired intestinal barrier function (low fecal sIgA and EPX). Patients in this zone have higher rates of opportunistic infections (e.g. *Blastocystis spp.* & *Dientamoeba fragilis*) as well as fecal fat malabsorption. Commensal abundance is higher in this group suggesting potential bacterial overgrowth.

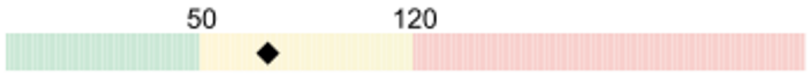

Healthy-Pattern Continuum*
10
8
6
4
2
0
You
0
4
8
12
16
20
24
Reference Variance Score**


-50%
-25%
Healthy Cohort
+25%
Bacteroidetes Phylum
Increase in *Bacteroides* spp. and *Odoribacter* spp. seen in animal-based diets; *Prevotella* increased with plant-based diet
Firmicutes Phylum
Contains many butyrate-producers; most species responsive to plant-based diets; *Faecalibacterium* spp. is anti-inflammatory
Actinobacteria Phylum
Bifidobacterium is increased with plant-based diets; *Collinsella* may be proinflammatory, and is elevated with a Western-diet
Proteobacteria Phylum
Some species may be proinflammatory; *E. coli* consumes simple sugars and is lower in individuals on plant-based diets
Euryarchaeota Phylum***
Methanobrevibacter smithii is associated with methane production and with diets high in carbohydrates
Fusobacteria Phylum
Certain *Fusobacterium* spp. may be proinflammatory and increased on low fiber, high fat diets
Verrucomicrobia Phylum
Akkermansia spp. is involved in gut membrane integrity and may be increased with polyphenols and prebiotics

Methodology: GC-FID, Automated Chemistry, EIA

	Result	QUINTILE DISTRIBUTION (1st 2nd 3rd 4th 5th)	Reference Range
Digestion and Absorption			
Pancreatic Elastase 1 †	360	100 200	>200 mcg/g
Products of Protein Breakdown (Total*) (Valerate, Isobutyrate, Isovalerate)	4.4		1.8-9.9 micromol/g
Fecal Fat (Total*)	26.2		3.2-38.6 mg/g
Triglycerides	2.5		0.3-2.8 mg/g
Long-Chain Fatty Acids	18.6		1.2-29.1 mg/g
Cholesterol	3.7		0.4-4.8 mg/g
Phospholipids	1.4		0.2-6.9 mg/g

Inflammation and Immunology

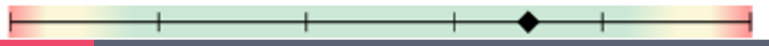
Calprotectin †	72 H		<=50 mcg/g
Eosinophil Protein X (EPX)†	1.9		<=4.6 mcg/g
Fecal secretory IgA	1,104		<=2,040 mcg/mL

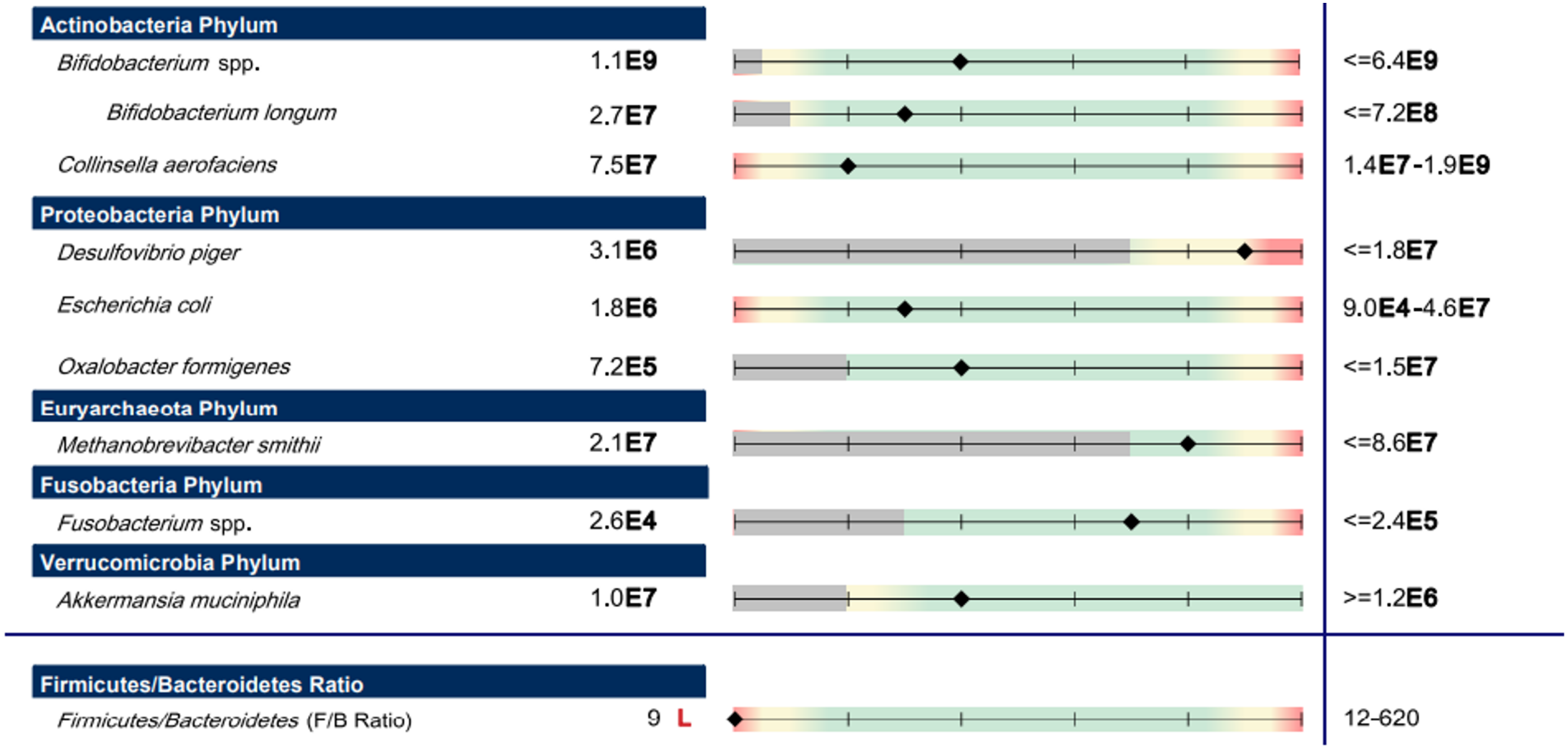
Gut Microbiome Metabolites

Metabolic

Short-Chain Fatty Acids (SCFA) (Total*) (Acetate, n-Butyrate, Propionate)	43.1		>=23.3 micromol/g
n-Butyrate Concentration	7.4		>=3.6 micromol/g
n-Butyrate %	17.2		11.8-33.3 %
Acetate %	59.5		48.1-69.2 %
Propionate %	23.2		<=29.3 %
Beta-glucuronidase	3,106		368-6,266 U/g

Commensal Bacteria (PCR)

	Result CFU/g stool		QUINTILE DISTRIBUTION 1st 2nd 3rd 4th 5th	Reference Range CFU/g stool
Bacteroidetes Phylum				
Bacteroides-Prevotella group	4.4**E8**			3.4**E6**-1.5**E9**
Bacteroides vulgatus	1.3**E9**			<=2.2**E9**
Barnesiella spp.	1.2**E8**			<=1.6**E8**
Odoribacter spp.	1.8**E8**	H		<=8.0**E7**
Prevotella spp.	3.3**E7**	H		1.4**E5**-1.6**E7**
Firmicutes Phylum				
Anaerotruncus colihominis	9.7**E6**			<=3.2**E7**
Butyrivibrio crossotus	9.4**E4**			5.5**E3**-5.9**E5**
Clostridium spp.	3.1**E9**			1.7**E8**-1.5**E10**
Coprococcus eutactus	9.9**E6**			<=1.2**E8**
Faecalibacterium prausnitzii	2.1**E9**			5.8**E7**-4.7**E9**
Lactobacillus spp.	1.6**E8**			8.3**E6**-5.2**E9**
Pseudoflavonifractor spp.	2.6**E8**	H		4.2**E5**-1.3**E8**
Roseburia spp.	6.6**E8**			1.3**E8**-1.2**E10**
Ruminococcus spp.	4.4**E7**	L		9.5**E7**-1.6**E9**
Veillonella spp.	1.4**E7**			1.2**E5**-5.5**E7**

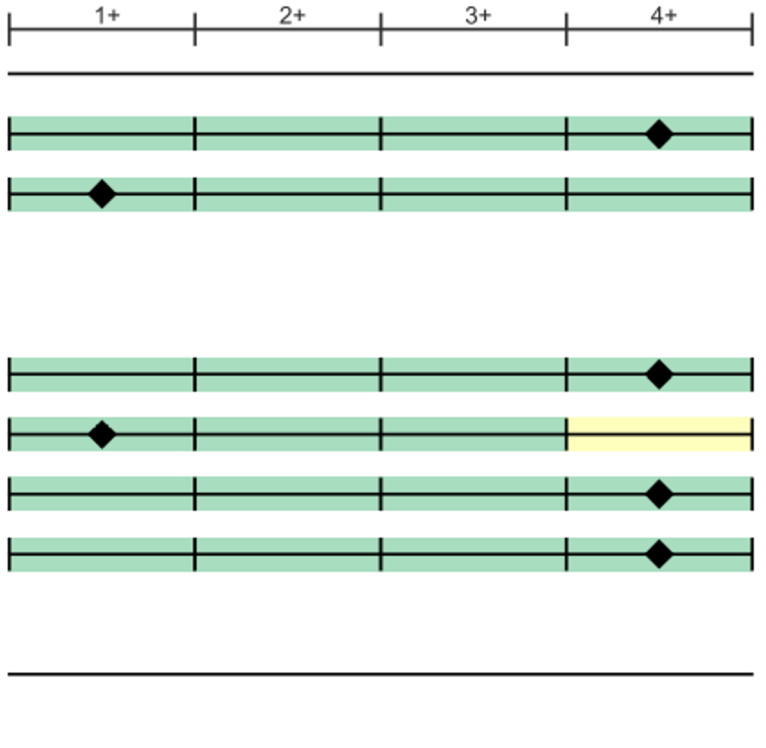


FUNCTIONAL MEDICINE
Continuing Education

Microbiology Legend

NG	NP	PP	P
No Growth	Non-Pathogen	Potential Pathogen	Pathogen

Bacteriology (Culture)



Lactobacillus spp.		NG
Escherichia coli	4+	NP
Bifidobacterium	1+	NP

Additional Bacteria

alpha haemolytic Streptococcus	4+	NP
Staphylococcus aureus	1+	NP
Haemolytic Escherichia coli	4+	NP
Enterococcus faecalis	4+	NP

Mycology (Culture)

NG

Organism	Result	Units		Expected Result
Blastocystis spp.	<2.14e2	femtograms/microliter C&S stool	Not Detected	Not Detected
Cryptosporidium parvum/hominis	<1.76e2	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	<1.84e2	genome copies/microliter C&S stool	Not Detected	Not Detected
Entamoeba histolytica	<9.64e1	genome copies/microliter C&S stool	Not Detected	Not Detected
Giardia	<1.36e1	genome copies/microliter C&S stool	Not Detected	Not Detected

Other Labs

- TSH 1.710 uIU/ml
- T4 Free 1.52 ng/dl
- T3, Free 2.8 pg/ml
- Reverse T3 16.5 ng/dl
- Iron Bind Cap (TIBC) 361 ug/dl
- UIBC 216 ug/dl
- Iron 145 ug/dl
- Iron Saturation 40%
- Free Insulin 6.9% uU/ml
- Total Insulin 6.9 uU/ml
- Vitamin D 35.2 ng/ml
- Ferritin 31 ng/ml

Break-Out Time

1. What labs are out of range for Carla?
    1. Any labs in range, but sub-optimal?
    2. What replacement strategies?
2. Thinking about a 5-R protocol, what would you recommend for her?
    1. Remember 5-R Stands for..
        1. Remove
        2. Replace
        3. Reinoculate
        4. Repair
        5. Rebalance
3. Any dietary recommendations for Carla?

Wrapping Up

Take-Home Points

- IBS and IBD have different pathologies but can have similar treatment approaches with functional medicine principles
- Inflammation can be present in both, however it is more likely to be present in IBD, and needs targeted nutritional support.
- Addressing root causes including dysbiosis, inflammation, stress, etc can improve symptoms and potentially reverse disease progression.