

TREATMENT GUIDE FOR CLINICIANS

Gut Conditions

OVERVIEW

Many gut conditions are associated with changes in the microbiome. The SmartGut report provides information on the following: irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), and constipation and associated symptoms.

IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder. The underlying cause is still not fully understood, although it is proposed as a set of symptoms resulting from diverse pathologies rather than a disease itself [1]. There are several subtypes of IBS including IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), mixed (IBS-M), and unclassified. Initial treatment may include dietary and lifestyle changes, such as a low fermentable sugar (fermentable oligo-, di-, mono-saccharides and polyols, or "FODMAPS") diet, or avoiding lactose or gluten. Patients with more severe symptoms may benefit from pharmacologic therapy to address predominant symptoms. Studies show that patients with IBS have an underlying dysbiosis of their microbiome, which presents a novel target for monitoring and treatment [2,3].

INFLAMMATORY BOWEL DISEASE: CROHN'S DISEASE & ULCERATIVE COLITIS

Inflammatory bowel disease (IBD), considered a multifactorial disorder, is characterized by chronic inflammation of the distal gut [4]. IBD includes two main subtypes, ulcerative colitis (UC) and Crohn's disease (CD). In UC, inflammation is limited to the colorectal region and the lining of the colon while CD can be found in all sites of the GI tract and is transmural. IBD is multifaceted with host genetic factors, the host immune system, and environmental factors playing a role in disease [5]. Diagnosis of IBD may require many tests, including blood work, radiology, and colonoscopy with biopsies. The microbiome in patients with IBD is significantly altered with decreased microbial diversity and an altered microbial composition [6-11] and the microbiome is an emerging treatment area for IBD patients.

CONSTIPATION, ABDOMINAL TENDERNESS, BLOATING, FLATULENCE

Constipation is a common chronic condition characterized by infrequent stools and/or difficult passage of stools [12]. After secondary causes are ruled out, management of primary chronic constipation may include dietary and lifestyle changes, as well as medication such as fiber supplements, laxatives, stool-softeners, and osmotic agents. Studies suggest a correlation between alterations in the gut microbiome and primary chronic constipation, which may provide new and effective treatments for patients [13,14].

INDICATIONS FOR SMARTGUT TESTING

- Diagnosis or clinical suspicion of IBS or IBD
- Constipation not responding to dietary changes or medications
- Associated symptoms: constipation, diarrhea, abdominal pain, abnormal stool frequency, abnormal stool form, abnormal stool passage, abdominal bloating, mucous in stool

RELEVANT SMARTGUT RESULTS

IRRITABLE BOWEL SYNDROME

- Low microbial diversity [15-19]
- High levels of one or more of the following microorganisms: *Campylobacter*, *Escherichia-Shigella*, *Salmonella enterica* and *Veillonella* [20,21]
- Low levels of one or more of the following microorganisms: *Alistipes*, *Bifidobacterium*, *Collinsella aerofaciens* and *Lactobacillus* [21-25]

INFLAMMATORY BOWEL DISEASE

- Low microbial diversity [26-28]
- High levels of one or more of the following microorganisms: *Desulfovibrio piger* and *Fusobacterium* [29,30]
- Low levels of: *Roseburia* [31]

ULCERATIVE COLITIS

- Low microbial diversity [26-28]
- High levels of: *Ruminococcus* [32]
- Low levels of one or more of the following microorganisms: *Akkermansia muciniphila* [32], *Odoribacter* [31], *Prevotella* [26,33,34], *Roseburia* [35], *Ruminococcus albus* [36]

CROHN'S DISEASE

- Low microbial diversity [26-28]
- High levels of one or more of the following microorganisms: *Escherichia-Shigella* [31,37,38] *Ruminococcus* [32,33]
- Low levels of one or more of the following microorganisms: *Akkermansia muciniphila* [32], *Bifidobacterium* [39], *Dialister invisus* [39], *Odoribacter* [31], *Roseburia* [33,39]

CONSTIPATION, ABDOMINAL TENDERNESS, BLOATING, FLATULENCE

- High levels of one or more of the following microorganisms: *Methanobrevibacter smithii* [40,41], *Anaerotruncus colihominis* [42], *Bacteroides fragilis* [43]
- Low levels of: *Bifidobacterium* [44]

CLINICAL TREATMENT SUGGESTIONS BASED ON SMARTGUT RESULTS

IRRITABLE BOWEL SYNDROME - INTERVENTIONS TO CONSIDER:

- **Consider dietary changes:** If clinically appropriate, a low FODMAP diet may be beneficial to control IBS symptoms; more studies are needed to determine if alterations in the microbiome are beneficial long-term [15,45].
- **Consider the use of nonabsorbable antibiotic such as rifaximin:** Studies have shown this may alleviate IBS symptoms by treating the underlying dysbiosis [18,46].
- **Increase probiotics:** If clinically appropriate, probiotics such as *Bifidobacterium* and *Lactobacillus* have been shown to be effective in improving IBS symptoms; the specific type is still unknown [18,47]. The following probiotics have been studied and shown to improve IBS symptoms:
 - *Bifidobacterium infantis* 35624 1x10¹⁰ [48,49]
 - *Lactobacillus plantarum* 299V (LP299V) [50]
 - *Lactobacillus acidophilus*-SDC 2012, 2013 [51]
 - *Escherichia coli* Nissle 1917 [52]
 - *L. rhamnosus*, *E. faecium*, *L. acidophilus*, and *L. plantarum* (Symprove) [53]
 - VSL#3 (*L. casei*, *L. plantarum*, *L. acidophilus*, *L. delbrueckii*, *B. longum*, *B. breve*, *B. infantis*, *S. salivarius*) [54]
- **Consider avoiding NSAIDs and PPIs:** Patients with IBS have higher rates of prior use of these medications, which may alter the microbiome and impact IBS symptoms [55].

ULCERATIVE COLITIS - INTERVENTIONS TO CONSIDER:

- **Suggest a diet with less meat and more fruits/vegetables:** Vegetable and fruit intake is associated with a lower risk for UC [56,57]. A high-meat diet is associated with overgrowth of sulfate reducing bacteria (*Desulfovibrio*), which are also found in patients with UC [36]. Meat protein is high in sulfur which might increase the risk for relapse [58, 59].
- **Suggest a diet with more fiber and/or prebiotics:** If clinically appropriate, increased dietary fiber intake may be beneficial for UC patients. Fiber provides nourishment for bacteria in the distal gut, which otherwise may digest human mucins and other polysaccharides leading to damage of the tight junction barrier [60]. Fiber is also processed by gut bacteria into butyrate which may have anti-inflammatory properties. Intake of more fiber may result in increased abundance of beneficial bacteria, increased butyrate production, and decreased disease parameters such as disease parameters such as C-reactive protein (CRP). Note that the intake of more fiber by UC patients might initially lead to increased flatulence [61], but long term effects have proven to decrease disease severity for many patients. Fibers with demonstrated benefit in UC patients include:
 - **Wheat bran:** 16 gram per day [62]
 - **Oat bran:** 60 gram per day [63]
 - **Germinated barley foodstuff** (protein and fiber rich product made from malt; 30 gram per day) [64-70]

- **Consider probiotics:** If clinically appropriate, probiotics may be beneficial to UC patients. VSL#3, a probiotic mixture of *Lactobacillus*, *Bifidobacterium*, and *Streptococcus thermophilus*, appears to be consistently beneficial in UC at a dose of 3,600 billion CFU per day (VSL Pharmaceuticals, MD; two sachets twice a day, each sachet contains 900 billion viable bacteria) [69,71-78].
- **Increase turmeric:** Curcumin, the biologically active substance in the spice turmeric, may potentially confer benefit at a dose of 2 to 3 grams per day [79,80].
- **Suggest a SCD diet:** Consider if clinically appropriate. The Specific Carbohydrate Diet has been successful in particular with pediatric IBD patients. In this diet, all grains, sugars, processed foods, and dairy are excluded, although honey, specific home-made yogurt, and hard cheeses are allowed. The SCD diet has also been successful in pediatric and adult UC patients [81-83].
- **Increase polyphenols:** Animal studies suggest dietary polyphenols, such as those found in coffee [84], grapes [85], green tea [86] and cocoa [87] may prevent or reduce colitis (88). Consider increasing if clinically appropriate.
- **Advise against a low FODMAP diet:** A low FODMAP diet (which eliminates fructans) can lead to short term improvements (e.g. less gas and bloating) but does not appear to be beneficial in the long term or on intestinal dysbiosis [61].
- **Stool transplants:** Fecal microbiota transplantation (FMT) is a procedure in which fecal material from a healthy donor is administered to the intestinal tract of a recipient, often after a colon cleanout to remove the host's microbiota [89]. In the US and Canada, FMT is currently only FDA approved as a treatment for recurrent *Clostridium difficile* infections; it may be considered only under appropriate experimental protocol for other conditions. In clinical studies, FMT is moderately successful in UC [90-94]. However, results in other studies were less successful [95-97].

CROHN'S DISEASE - INTERVENTIONS TO CONSIDER:

- **Suggest dietary changes:** The consumption of meats and sweets have been associated with a higher CD risk, while vegetable, fruit, and fiber consumption is associated with a lower risk for IBD, including Crohn's disease [56,57]. The abundance of several short-chain fatty acid (e.g. butyrate) producers is decreased in CD, and dietary components that will increase the SCFA producers might counteract the disease [59]. Intake of dietary fiber is associated with reduced disease flares in patients with Crohn's disease [98].
- **Suggest a SCD diet:** Consider if clinically appropriate. The Specific Carbohydrate Diet has been successful in particular with pediatric IBD patients. In this diet, all grains, sugars, processed foods, and dairy are excluded, although honey, specific home-made yogurt, and hard cheeses are allowed. The SCD diet has been successful in pediatric CD patients [81,82,99].
- **Test for and treat for vitamin D deficiency:** Vitamin D deficiency has been found to be associated with an increased risk for IBD. Low vitamin D levels are commonly found in both CD and UC patients and are associated with disease severity. Testing and treating for low vitamin D levels might be beneficial for IBD patients [100-102].
- **Consider avoiding maltodextrin:** Maltodextrin is a common food additive present in many packaged food items including breakfast cereals, potato chips, jerky, and artificial sweeteners (often listed under the name "modified starch") [103].

- **Neutral advice about prebiotics and probiotics:** Unlike positive findings with UC patients, probiotics have shown little effect in Crohn's disease patients [73]. Similarly, while prebiotics have shown clear improvements of clinical symptoms in UC, their effects in CD are less clear. Fructo-oligosaccharides (FOS) appear to have little to no effect in CD patients, with no *Bifidobacterium* increase and little relief of clinical symptoms or remission [104-105]. However, in a different study where CD patients received oligofructose-enriched inulin, an increase in *Bifidobacteria* was associated with reduction of disease severity [106].
- **Stool transplants:** Fecal microbiota transplantation (FMT) is a procedure in which fecal material from a healthy donor is administered to the intestinal tract of a recipient, often after a colon cleanout to remove the host's microbiota [89]. In the US and Canada, FMT is currently only FDA approved as a treatment for recurrent *Clostridium difficile* infections; it may be considered only under appropriate experimental protocol for other conditions. In clinical studies, FMT is moderately successful in CD patients [107-111].

CONSTIPATION - INTERVENTIONS TO CONSIDER:

- **Increase fiber in diet:** Fiber increases stool bulk and increases motility [112]. If clinically appropriate, consider including 20-35 g/day of fiber including foods and raw bran.
- **Increase prebiotics:** If clinically appropriate, prebiotics may stimulate growth of *Lactobacilli* and *Bifidobacteria* and help generate regular bowel movements [113,114]. Sources of prebiotic fiber include soybeans, inulins, unrefined grains, and non-digestible oligosaccharides. One study showed a supplement of 15g/day of combination inulin and partially hydrolyzed guar gum led to improvement in constipation and a decrease in potentially pathogenic *Clostridium*.
- **Increase probiotics:** If clinically appropriate, probiotics may improve the number of stools per week by altering the gut microbiota and increasing motility [115]. Studies demonstrate the following regimens to be effective for reducing symptoms of constipation:
 - Probiotic foods:
 - Daily probiotic drink of *L. casei* Shirota containing at least 6.5×10^9 CFU [116-117]
 - Daily consumption of fresh cheese with added *B. lactis* Bi-07 with 10^8 CFU per serving [118]
 - Daily fermented milk drink containing *B. lactis* DN-173010 (1.25×10^{10} CFU) mixed with classical yogurt with *S. thermophilus* and *L. bulgaricus* [119]
 - Daily milk-like drink with *B. lactis* GCL2505 [120]
 - Consumption of artichokes (180g) enriched with *L. paracasei* IMPC 2.1 (2×10^{10} CFU) [121]
 - Probiotic supplements:
 - Daily probiotic supplement of *B. lactis* HN019 at a high dose (17.2 billion CFU) or low dose (1.8 billion CFU) [122]
 - Daily probiotic containing *L. plantarum* and *B. breve* (2.5×10 CFU of each strain), or *B. lactis* BS01 (5×10 CFU) significantly improved constipation [123]
 - Twice daily *L. reuteri* (DSM 17938) at a dose of 10^8 CFU [124]
- **Avoid proton pump inhibitors:** Proton pump inhibitors can cause constipation, and may directly impact the microbiome [125].

POTENTIAL OUTCOMES

- Improved patient gastrointestinal health and reduced comorbidities
- Potentially decrease the need for additional medication and intervention

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