TREATMENT GUIDE FOR PHYSICIANS

Gut Conditions & Symptoms

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), infectious diarrhea, asymptomatic diverticulosis, and common gastrointestinal symptoms.

INFECTIOUS DIARRHEA
Infections are a common cause of gastrointestinal symptoms worldwide [1,2]. SmartGut tests for several pathogenic microorganisms including Clostridium difficile, Campylobacter, Escherichia-Shigella, Salmonella enterica, and Vibrio cholerae. Please note that SmartGut is indicated for patients with chronic conditions and symptoms rather than acute symptoms of less than four weeks duration.

Certain pathogens that may cause acute diarrheal illness are also implicated in post-infectious chronic conditions. For example, Salmonella, Shigella, and Campylobacter are positively associated with sudden-onset forms of IBS [1,3-6]. Campylobacter is also believed to be a predisposing agent in IBD [1,7,8]. In addition, the relative abundance of Escherichia coli is often increased in the stool of patients with ulcerative colitis (UC) and Crohn’s disease (CD) [9-13]. The gut microbiome may play a role in risk of gastrointestinal infections as well as risk of related complications.

IRRITABLE BOWEL SYNDROME
Irritable bowel syndrome 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 [14]. 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-, monosaccharides and polyols, or “FODMAPS”) diet, or avoiding lactose or gluten.
IRRITABLE BOWEL SYNDROME (CONT.)
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 [15,16].

INFLAMMATORY BOWEL DISEASE: CROHN’S DISEASE & ULCERATIVE COLITIS
Inflammatory bowel disease, considered a multifactorial disorder, is characterized by chronic inflammation of the gut [17]. 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 [18]. 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 [11,19-23] and the microbiome is an emerging treatment area for IBD patients.

CONSTIPATION, ASYMPTOMATIC DIVERTICULOSIS, ABDOMINAL TENDERNESS, BLOATING, FLATULENCE
Constipation is a common chronic condition characterized by infrequent stools and/or difficult passage of stools [24]. 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.

Asymptomatic diverticulosis is characterized by small diverticula in the wall of the colon, and (when it becomes symptomatic) is associated with increased risk for bleeding, diverticulitis and related complications (such as pain, obstruction, and constipation). Pathogenesis of diverticulosis is unclear, with mixed evidence as to the role of fiber and primary constipation; abnormal colonic motility [25] may contribute to development of diverticula, as well as genetic and environmental factors [26-28].

Studies suggest a correlation between alterations in the gut microbiome and primary chronic constipation [29-32], asymptomatic diverticulosis [33], abdominal pain [34,35], bloating [34], and flatulence [36], which may provide new and effective treatments for patients [37,38].
INDICATIONS FOR SMARTGUT TESTING

- Diagnosis or clinical suspicion of IBS or IBD
- Diagnosis or clinical suspicion of diverticulosis
- Chronic diarrhea not responding to treatment
- Constipation not responding to dietary changes or medications
- Diarrhea, abdominal pain, nausea, change in stool habits, abnormal stool consistency (according to the Bristol stool scale [39])

RELEVANT SMARTGUT RESULTS

Infectious Diarrhea

- Presence of at least one of the following pathogenic microorganisms:
  - *Clostridium difficile* [40,41]
  - *Campylobacter* [1,40,42]
  - *Escherichia/Shigella* [40,43]
  - *Salmonella enterica* [40,43]
  - *Vibrio cholerae* [40,44]
- High levels of: *Bacteroides fragilis* [45,46], *Clostridium* [47,48]
- Low levels of: *Lactobacillus* [49]
- Low microbial diversity [50,51]

Irritable Bowel Syndrome

- High Significance Index

    - High levels of one or more of the following microorganisms: *Campylobacter* [3], *Escherichia/Shigella* [3], *Salmonella enterica* [52], *Methanobrevibacter smithii* [53], *Veillonella* [54].

    - Low levels of one or more of the following microorganisms: *Alistipes* [55], *Bifidobacterium* [56], *Collinsella aerofaciens* [4,57,58], *Paraprevotella* [55], *Lactobacillus* [54].
RELEVANT SMARTGUT RESULTS (CONT.)

Inflammatory Bowel Disease

- High levels of one or more of the following microorganisms: *Desulfovibrio piger* [59], *Fusobacterium* [60], *Campylobacter* [61]
- Low levels of: *Roseburia* [62]

Crohn’s Disease

- High Significance Index
  - High levels of one or more of the following microorganisms: *Clostridium* [62,63], *Clostridium difficile* [64], *Escherichia/Shigella* [62], *Methanobrevibacter smithii* [65], *Parabacteroides* [63]
  - Low levels of one or more of the following microorganisms: *Akkermansia muciniphila* [66], *Bacteroides* [65,67], *Bacteroides fragilis* [67], *Bifidobacterium* [63,65,67], *Dialister invisus* [68], *Lactobacillus* [65], *Odoribacter* [62], *Phascolarctobacterium* [62], *Prevotella* [67], *Roseburia* [62], *Ruminococcus* [65]
- Low microbial diversity [19]

Ulcerative Colitis

- High Significance Index
  - High levels of one or more of the following microorganisms: *Campylobacter* [61, 63, 69], *Clostridium* [62], *Clostridium difficile* [23,64], *Methanobrevibacter smithii* [65], *Ruminococcus albus* [70], *Salmonella enterica* [52].
  - Low levels of one or more of the following microorganisms: *Akkermansia muciniphila* [66], *Bacteroides* [65,67], *Bacteroides fragilis* [67], *Bifidobacterium* [65, 67], *Lactobacillus* [65], *Odoribacter* [62], *Phascolarctobacterium* [62], *Prevotella* [67], *Roseburia* [62], *Ruminococcus* [65].
- Low microbial diversity [9]

Constipation, Abdominal Pain, Bloating, Flatulence

- High levels of one or more of the following microorganisms: *Anaerotruncus colihominis* [34], *Butyrivibrio crossotus* [34], *Butyrivibrio* [30,31], *Coprococcus* [30, 31], *Faecalibacterium* [31], *Gelria* [30], *Holdemania* [30], *Methanobrevibacter smithii* (in constipation) [32], *Paraprevotella* [30], *Phascolarctobacterium* [30], *Ruminococcus flavocaciens* [34], *Veillonella* [57], *Bacteroides fragilis* [36], *Blautia* [36], *Clostridium* [36], *Coprococcus* [36], *Phascolarctobacterium* [36]
RELEVANT SMARTGUT RESULTS (CONT.)

Constipation, Abdominal Pain, Bloating, Flatulence (cont.)

• Low levels of one or more of the following microorganisms: *Bifidobacterium* [29], *Methanobrevibacter smithii* (in abdominal pain [35]), *Oscillospira* [36], *Roseburia* [30,31], *Ruminococcus* [34]

Asymptomatic Diverticulosis

• Low levels of: *Akkermansia muciniphila* [33]

CLINICAL TREATMENT SUGGESTIONS BASED ON SMARTGUT RESULTS

Infectious Diarrhea - Interventions to Consider:

• **Antibiotics:** Patients with positive results for any pathogenic microorganisms should meet and discuss this with their physician and be treated with appropriate antibiotics as defined by current standard of care.

• **Consider the use of probiotics, prebiotics or synbiotics:** A systematic review of the evidence showed the use of probiotics can help to prevent *C. difficile* associated diarrhea [71]. Another meta-analysis suggested that probiotics can also prevent traveler’s diarrhea [72], an infection affecting travelers caused by different pathogens, including *Escherichia coli* and *Salmonella*. Additional studies also suggested that prebiotics can protect against gastrointestinal pathogens [73].

• **Consider a fiber-rich diet:** A preliminary study made in mice containing human gut microbiota [74] showed that the deprivation of fiber in the diet made the mice more susceptible to a pathogen-induced colitis. The regular consumption of fiber-rich products such as vegetables and grains can help the microbiome protect against pathogens.

• **Consider a fecal microbiota transplantation (FMT):** The use of FMT has been described to be effective for the treatment of *C. difficile* infection [75]. This practice is approved and regulated by the FDA for recurrent *C. difficile* infection; FMT is considered investigational for all other conditions and requires an appropriate permit [76].

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 [77,78].
**Irritable Bowel Syndrome - Interventions to Consider (cont.):**

- **Consider the use of a nonabsorbable antibiotic such as rifaximin:** Studies have shown this may alleviate IBS symptoms by treating the underlying dysbiosis [79,80].

- **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 [79,81]. The following probiotics have been studied and shown to improve IBS symptoms:
  - *Bifidobacterium infantis* 35624 1x10¹⁰ [82,83]
  - *Lactobacillus plantarum* 299V (LP299V) [84]
  - *Lactobacillus acidophilus*-SDC 2012, 2013 [85]
  - *Escherichia coli Nissle* 1917 [86]
  - *L. rhamnosus, E. faecium, L. acidophilus, and L. plantarum* (Symprove) [87]
  - VSL#3 (*Lactobacillus casei, L. plantarum, L. acidophilus, Lactobacillus delbrueckii, Bifidobacterium longum, Bifidobacterium breve, B. infantis, Streptococcus salivarius*) [88]

- **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 [89].

**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 [90,91]. A high-meat diet is associated with overgrowth of sulfate-reducing bacteria (*Desulfovibrio*), which are also found in patients with UC [70]. Meat protein is high in sulfur which might increase the risk for relapse [92,93].

- **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 [94]. Fiber is also processed by gut bacteria into short-chain fatty acids (e.g. butyrate) which may have anti-inflammatory properties. Intake of more fiber may result in increased abundance of beneficial bacteria, increased short-chain fatty acid production, and decreased disease parameters such as C-reactive protein (CRP).
CLINICAL TREATMENT SUGGESTIONS BASED ON SMARTGUT RESULTS (CONT.)

- **Suggest a diet with more fiber and/or prebiotics (cont.):** Note that the intake of more fiber by UC patients might initially lead to increased flatulence [95], but long-term effects have proven to decrease disease severity for many patients. Fibers with demonstrated benefit in UC patients include:
  - Wheat bran: 16 grams per day [96]
  - Oat bran: 60 grams per day [97]
  - Germinated barley foodstuff (protein and fiber-rich product made from malt; 30 grams per day) [98-104]

- **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) [103,105-112].

- **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 [113,114].

- **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 homemade yogurt, and hard cheeses are allowed. The SCD diet has also been successful in pediatric and adult UC patients [115-117].

- **Increase polyphenols:** Animal studies suggest dietary polyphenols, such as those found in coffee [118], grapes [119], green tea [120] and cocoa [121] may prevent or reduce colitis [122]. 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 [95].

- **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 [123].
CLINICAL TREATMENT SUGGESTIONS BASED ON SMARTGUT RESULTS (CONT.)

Ulcerative Colitis - Interventions to Consider (cont.):

• **Stool transplants (cont.):** 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 [124-128]. However, results in other studies were less successful [129-131].

Crohn's Disease - Interventions to Consider:

• **Suggest dietary changes:** The increased consumption of meats and refined sugars has 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 [90,91]. 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 [93]. Intake of dietary fiber is associated with reduced disease flares in patients with Crohn's disease [132].

• **Suggest an 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 homemade yogurt, and hard cheeses are allowed. The SCD diet has been successful in pediatric CD patients [115,116,133].

• **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 [134-136].

• **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”) [137].

• **Neutral advice about prebiotics and probiotics:** Unlike positive findings with UC patients, probiotics have shown little effect in Crohn's disease patients [107]. 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 [138,139]. However, in a different study where CD patients received oligofructose-enriched inulin, an increase in *Bifidobacteria* was associated with reduction of disease severity [140].
CLINICAL TREATMENT SUGGESTIONS BASED ON SMARTGUT RESULTS (CONT.)

Crohn's Disease - Interventions to Consider (cont.):

- **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 [123]. 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 [141-145].

Constipation and Asymptomatic Diverticulosis - Interventions to Consider:

- **Increase fiber in diet**: Fiber increases stool motility [146] and plays a questionable role in preventing the development of new diverticula, diverticulitis, or diverticular bleeding. 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 [147,148]. Sources of prebiotic fiber include soybeans, inulins, unrefined grains, and non-digestible oligosaccharides.

- **Increase probiotics**: If clinically appropriate, probiotics may improve the number of stools per week by altering the gut microbiota and increasing motility [149]. 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 $6.5 \times 10^9$ CFU [150,151]
    - Daily consumption of fresh cheese with added *B. lactis* Bi-07 with 108 CFU per serving [152]
    - Daily fermented milk drink containing *B. lactis* DN-173010 (1.25 x1010 CFU mixed with classical yogurt with *S. thermophilus* and *L. bulgaricus* [153]
    - Daily milk-like drink with *B. lactis* GCL2505 [154]
    - Consumption of artichokes (180g) enriched with *L. paracasei* IMPC 2.1 (2x1010 CFU) [155]
  - **Probiotic supplements**:
    - Daily probiotic supplement of *B. lactis* HNO19 at a high dose (17.2 billion CFU) or low dose (1.8 billion CFU) [156]
    - Daily probiotic containing *L. plantarum* and *B. breve* (2.5 x 10 CFU of each strain), or *B. lactis* BS01 (5 x 10 CFU) significantly improved constipation [157]
    - Twice daily *L. reuteri* (DSM 17938) at a dose of 108 CFU [158]
CLINICAL TREATMENT SUGGESTIONS BASED ON SMARTGUT RESULTS (CONT.)

Constipation and Asymptomatic Diverticulosis - Interventions to Consider (Cont):
• Avoid proton pump inhibitors: Proton pump inhibitors can cause constipation, and may directly impact the microbiome [159].

POTENTIAL OUTCOMES
• Improved patient gastrointestinal health and reduced comorbidities
• Potentially decrease the need for additional medication and intervention
REFERENCES

REFERENCES


[37] Y. Zhao, Y.-B. Yu, Springerplus 5 (2016) 1130.


REFERENCES


[76] https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm361379.htm


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