Microbial Influences on Irritable Bowel Syndrome

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KEYWORDS

• Irritable bowel syndrome • Postinfection irritable bowel syndrome • Microbiome • Metabolome • Small intestinal bacterial overgrowth

KEY POINTS

- The potential for microbes to influence the development of irritable bowel syndrome (IBS) is exemplified by the widely described phenomenon of postinfection IBS.
- Studies of the fecal microbiome in IBS have produced inconsistent results related to the heterogeneity of the condition, variations in diet, symptom severity, and treatment.
- The status of small intestinal bacterial overgrowth in IBS remains controversial with the interpretation of many studies complicated by methodological limitations.
- Studies of the small intestinal microbiome and metabolome in IBS show promise in explaining the pathophysiology of symptoms characteristic of IBS.

THE ORIGINS OF THE MICROBIAL HYPOTHESIS IN IRRITABLE BOWEL SYNDROME—POSTINFECTION IRRITABLE BOWEL SYNDROME

Reports of the development of chronic gastrointestinal symptoms in the aftermath of an apparently resolved enteric infection or infestation date back at least to the 1940s.[1,2] Stewart described the long-term outcome of cases of amebic dysentery seen in a military hospital in Sri Lanka and at the Tropical Diseases Center in Liverpool, UK.[2] Among them were a group, referred to as functional, type I, postdysenteric colitis (surely, the first description of postinfection irritable bowel syndrome [PI-IBS]), who, despite chronic symptoms, had normal or near normal appearances on sigmoidoscopic examination.[2] Twelve years later in what remains a classic description of irritable bowel syndrome (IBS), Chaudhary and Truelove reported that "in 34 (of 130) patients the symptoms dated from an attack of infective dysentery, either proven or strongly presumptive."[3] Beginning in the 1990s,[4] several series of varying size, design, and geographic origin delineated the prevalence, risk factors, and natural history of PI-

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Abbreviations	
CFU	colony forming unit
DGBI	disorders of gut-brain interaction
IBS	irritable bowel syndrome
IBS-C	irritable bowel syndrome with constipation
IBS-D	irritable bowel syndrome with diarrhea
IgE	immunoglobulin E
PI-IBS	postinfection irritable bowel syndrome
rRNA	ribosomal RNA
SIBO	small intestinal bacterial overgrowth

IBS. Some followed the outcome of large single source outbreaks resulting from food-borne or water-borne pathogens[5,6] while others calculated occurrence rates among those whose infection had been cataloged by a central reference laboratory or primary care database.[7,8] While many of these reports focused on bacterial infections, reports of PI-IBS following viral,[9] protozoal, and parasitic infections[10,11] began to appear. In 2017, a systematic review of PI-IBS that included 45 studies and over 21,000 individual cases[12] yielded an overall pooled prevalence of IBS following an episode of infections enteritis of 11.5%, very much in line with prior estimates.[13,14] PI-IBS was most likely to follow a protozoan or parasitic infection (event rate 41.9%) and least likely after a viral infection (6.4%) with rates following a bacterial infection being intermediate between these extremes at 13.8%. Females, those who suffered a severe index attack of enteritis, received antibiotic therapy and experienced psychological distress at the time of the infection were at greatest risk for the development of PI-IBS.[12] PI-IBS may not be a short-lived disturbance of bowel function with rates remaining high well beyond 12 months,[12] and up to 6 years in one study.[15]

Most recently, interest in this area has focused on the development of IBS-type symptoms in the aftermath of COVID-19 infections. While follow-up is still of relatively short duration, the evidence to date does indicate that there is an increased prevalence of IBS for up to 12 months following infection.[16–18]

More fundamental research on PI-IBS identified impacts on the microbiome, the immune response and the gut barrier (including increased permeability)[19,20]; findings that triggered the investigation of these parameters in IBS, in general, and provided much support for a role for the microbiome-gut-brain axis in IBS.

One hypothesis to explain PI-IBS posits that cross-reactivity between antibodies directed against the cytolethal distending toxin produced by *Campylobacter jejuni* and other bacteria that cause acute gastroenteritis and vinculin, an important cytoskeletal protein, leads to pathologic changes in the enteric nervous system, impaired motility, and an IBS-type phenotype.[21] In clinical studies, anti-cytolethal distending toxin and antivinculin antibodies showed promise in differentiating IBS with diarrhea (IBS-D) from inflammatory bowel disease, celiac disease, and control subjects.[22] In a subsequent study, results were less impressive with positivity rates for these antibodies ranging from 58% in IBS-D to 44% in mixed-type irritable bowel syndrme (IBS-M) and 27% in IBS with constipation (IBS-C) and with 16% of controls testing positive.[23] High rates of positivity for these antibodies have been reported among control subjects in another study, limiting their diagnostic value or pathophysiologic relevance.[24]

Aguilera-Lizarraga and colleagues provided an alternative hypothesis for PI-IBS. They have provided evidence that a bacterial infection and/or bacterial toxins can trigger an immune response that leads to the production of dietary-antigen-specific and gut localized immunoglobulin E (IgE) antibodies. Subsequent exposure to this

very same dietary antigen, to which the host had been tolerant prior to the infection, leads to an IgE-dependent and mast cell-dependent mechanism that provokes visceral pain.[25] This concept is intriguing as it combines 2 well-known phenomena in IBS—onset following infectious gastroenteritis and the induction of symptoms by food; to what extent it relates to IBS, in general, remains to be defined.

ENTER SMALL INTESTINAL BACTERIAL OVERGROWTH—THE SMALL INTESTINAL MICROBIOME IN IRRITABLE BOWEL SYNDROME

Small Intestinal Bacterial Overgrowth and Irritable Bowel Syndrome

The possibility of a relationship between small intestinal bacterial overgrowth (SIBO) and IBS emerged from a study demonstrating that a positive lactulose breath hydrogen test was more prevalent in patients with IBS than in healthy controls. Moreover, normalization of the test following antibiotic therapy was associated with the improvement in symptoms.[26] However, while the association between IBS and SIBO may hold when utilizing breath testing, this was not the case when small bowel aspirate and culture were employed to diagnose SIBO.[27,28] In addition, a positive lactulose breath test based on an early hydrogen peak may simply signify an abnormally rapid oro-cecal transit time, such as may accompany diarrhea-predominant IBS, rather than SIBO per se.[29] It has been suggested that the glucose breath test may be more accurate[30–32] in the detection of SIBO in this context but it, too, has its limitations.[33] Breath tests, therefore, need to be interpreted with great caution.[34,35] While the merits and limitations of the various methodologies employed to diagnose SIBO are critical to the definition of its presence and thus relevance to IBS symptomatology, their appraisal is beyond the scope of this review and can be found elsewhere.[36–38]

Nevertheless, one can envisage several mechanisms whereby a disturbed small intestinal microbiome could lead to the genesis of IBS symptoms such as pain, altered bowel function, and bloating. Changes in bile acid metabolism, short-chain fatty acid production or fermentation, all driven by bacteria or, in the case of methane, archaea, could all be invoked. Disruptions in bile acid physiology have been well described in IBS.[39] Suffice it to say that alterations in the composition of the fecal (and, thus, presumably, colonic) microbiota have been described in association with changes in bile acid physiology in subjects with IBS-D[40] but whether such changes are cause, consequence, or both remains to be established. Unfortunately, and for understandable reasons, microbiome-bile acid interactions in the small intestine, the proposed site of SIBO, remain largely a *terra incognita*.[41] It may be time to reconsider investigating the bile acid breath tests advocated for the diagnosis of SIBO decades ago and examine relationships between bile acid physiology and the small intestinal microbiome.[42]

Why Should Small Intestinal Bacterial Overgrowth Occur in Irritable Bowel Syndrome?

Of the various factors that protect against SIBO in health, alterations in small intestinal motor patterns could provide a basis for the development of SIBO in IBS. While little explored in recent years, evidence for dysmotility in IBS has been far from consistent.[43] Interestingly, Posserud and colleagues, while failing to document any difference in prevalence of SIBO between IBS and control subjects on the basis of the conventional 10^5 threshold for colony forming units (CFUs) on a jejunal aspirate, did note that SIBO, if defined using the lower threshold of 10^3 CFUs, was more common in IBS and linked to small bowel dysmotility.[27] That bacteria could injure the enteric neuromuscular apparatus and provide a basis for dysmotility and, potentially, SIBO, has already been discussed in the context of postinfection IBS.[23] Altered motility

has also been invoked to explain the observation that those, with IBS, who exhale methane in preference to hydrogen on a breath test and are thus presumed to harbor methanogens, such as *Methanobrevibacter smithii*, are more likely to have IBS-C than IBS-D[44] while those who exhale hydrogen sulfide are more likely to manifest diarrhea and harbor a higher relative abundance of H_2S-producing bacteria, including *Fusobacterium* and *Desulfovibrio* spp.[44]

In terms of other factors that predispose to SIBO, hypochlorhydria is not a feature of IBS, but patients are commonly prescribed proton pump inhibitors which have, to a variable extent, been linked with SIBO.[44–47]

In summary, the conditions that predispose to SIBO when it is diagnosed in the context of maldigestion and malabsorption (classical SIBO) are scarcely evident in IBS and their absence gives further reason to question the relationship between SIBO and IBS.

These concerns have not restrained speculation linking SIBO in IBS with other phenomena ranging from gut barrier dysfunction to immune activation and, via the microbiota-gut-brain axis, to effects on the central nervous system and describing a host of resultant scenarios such as “leaky gut,” “autoimmune disorders,” and “brain fog.” These associations flourish on the Internet and suffer from the same issue that has bedeviled the SIBO-IBS relationship—the accuracy of the definition of SIBO.

The Small Intestinal Microbiome and Metabolome

Until the normal small intestinal microbiome (and its metabolic products) is accurately defined, the relationship between IBS and SIBO will remain contentious. The good news is that modern high-throughput molecular microbiological approaches are now being applied to the small intestine.

Sundin and colleagues examined relationships between the fecal and the mucosal microbiomes of the duodenum and sigmoid colon and correlated these findings with the results of duodenal aspirate cultures and lactulose and glucose breath tests. While rates of breath test and duodenal aspirate culture positivity were similar in IBS patients and healthy controls, the bacterial composition of the duodenal and sigmoid colon mucosal microbiomes (but not the fecal microbiome) differed between those with positive and negative breath tests.[48] Leite and colleagues examined relationships between SIBO (defined as $> 10^3$ CFUs per mL) and the duodenal microbiome, analyzed using 16S ribosomal RNA (rRNA)-based sequencing, among individuals attending for upper gastrointestinal endoscopy for a variety of GI symptoms.[49] SIBO + subjects had higher bacterial counts, increased relative abundance of Proteobacteria and lower abundance of Firmicutes. Some correlations were evident between specific symptoms and members of phylum Proteobacteria and differences in metabolic pathways were also evident between SIBO and non-SIBO individuals.[49] Saffouri and colleagues[50] compared the results of aspiration and culture of small intestinal contents with an analysis of microbial community composition using 16S rRNA-based sequencing between individuals who had a variety of gastrointestinal symptoms with healthy controls. Although 52% had SIBO (vs none of the controls) and 16S rRNA-based sequencing revealed conspicuous differences between these same individuals and controls, the results of the 2 methodologies did not correlate. Indeed, “dysbiosis,” defined as being compositionally distinct from healthy individuals in beta diversity plots, and not the presence or absence of SIBO, was able to differentiate symptomatic from asymptomatic individuals. The small intestinal microbiota in the former was characterized by reduced diversity and decreased abundance of *Porphyromonas*, *Prevotella*, and *Fusobacterium* spp. They also noted differences in metabolic pathways; in this case, the evaluation of imputed functional pathways identified

that those involved in oxidative stress, biosynthesis of siderophores, and metabolism of simple sugars were enriched in symptomatic individuals whereas complex carbohydrate degradation pathways were less prevalent. More recently, Leite and colleagues performed another exploration of SIBO-microbiome relationships in a study on subjects attending for a diagnostic esophagogastroduodenoscopy by comparing conventional cultures with 16S and shotgun sequencing of bacteria in duodenal aspirates.[51] As the number of CFUs increased, microbial diversity and network connectivity decreased and the relative abundance of *Escherichia*/*Shigella* and *Klebsiella* increased. Indeed, 2 *E coli* strains and 2 *Klebsiella* species dominated the duodenal microbiome and were linked to symptoms. Their finding that *E coli* figured prominently in SIBO accords nicely with data from decades ago which emphasized the importance of this bacterium in the pathophysiology of malabsorption associated with SIBO.[52] There was no control (healthy) comparator population; instead, the subjects studied represented a heterogeneous population of individuals with a variety of gastrointestinal (GI) symptoms whose diet and medication use (such as proton pump inhibitor) may have varied. Is SIBO, as defined by the authors, relevant to their clinical presentation? Importantly, neither this study nor the Saffouri study[50] provide data on breath testing, the most commonly used modality to diagnose SIBO.

While coming to quite contrasting conclusions regarding the relevance of conventionally diagnosed SIBO to gastrointestinal symptoms, both the Leite[51] and Saffouri[50] studies provide guidance toward a brighter future for this fraught subject by indicating that a detailed analysis of the small intestinal microbiome and its metabolic activities may hold the key to understanding how bacteria in the small bowel may lead to symptoms.

The Impact of Antibiotics on Irritable Bowel Syndrome

What of the impact of treating SIBO on IBS symptoms? The efficacy of rifaximin and other antibiotics in ameliorating symptoms in IBS has been used as evidence to support an association between SIBO and IBS.[53] The interpretation of studies of antibiotic therapy for SIBO in IBS or SIBO in other contexts is not without its challenges. Several of these studies are either open-label or not placebo controlled.[38,54] Among randomized controlled trials, the original study from Pimentel's group used neomycin and reported a 75% improvement in symptoms among those who normalized their breath test.[55] In trials in disorders of gut-brain interaction (DGBI) 2 reported no impact on symptoms and low breath test normalization rates (20% and 22%) following a 10-day or 14-day course of rifaximin[56,57] and another, found no long-term impact on symptoms following a 10-day course of norfloxacin.[58] These studies also suffer from variations in disease population, mode of SIBO diagnosis, as well as the type, duration, and dose of antibiotic. The latter 2 are important given evidence for impact of both dose[59] and duration of therapy[60] on breath test normalization rates. Interestingly, rifaximin effects may also be influenced by the composition of the gut microbiome before therapy is initiated.[61]

On the other hand, rifaximin has been shown, albeit with a modest therapeutic gain, to alleviate symptoms in diarrhea IBS.[62] If the status of SIBO is uncertain in IBS and results of eradication and associated impact on symptoms unclear, then how does one explain these effects of rifaximin in IBS?

In short, the mechanism by which rifaximin offers benefit to patients with IBS remains unknown. While rifaximin might modulate the microbiome in the small bowel, it is also possible that microbiome-generated symptoms in IBS may be the result of abnormal colonic rather than small bowel fermentation[63] and that the efficacy of rifaximin is due to a reduction in fermentation in the colon and not in the small intestine[64] or

to nonmicrobial effects.[65] It is also interesting to note that while a positive lactulose breath test was predictive of the response to rifaximin in nondiarrhea IBS, post-treatment breath tests were not.[66]

There are clearly a number of unresolved issues here—one hopes that the application of modern microbiological methods coupled with novel capsule technologies for the dynamic measurement of intraluminal gases[67] and direct sampling of luminal content[68] will guide us forward.

THE GUT MICROBIOME IN IRRITABLE BOWEL SYNDROME—THE CHALLENGES

While one can develop convincing arguments to indicate how the gut microbiome and its interactions with the host could lead to perturbations that are potentially linked to the pathogenesis of symptoms in IBS, a consistent microbial signal characteristic of IBS has yet to emerge. Thus, while many studies provide evidence that microbiota are altered in those suffering from IBS, results are inconsistent.

Several factors may contribute to the variability between studies of the microbiome in IBS.

1. Methodological differences, such as the varying methods used to study and analyze microbiota composition. Up until recently, most studies were based on 16S high throughput sequencing which provides limited depth of coverage,
2. Variations in sample source, that is, fecal versus mucosal or colon versus small intestine; while the marked differences in both density and diversity between bacterial populations along the length of the GI tract have been recognized for many years, more recent studies have revealed significant differences between luminal and juxtamucosal microbial populations. In one study of 5 healthy individuals employing shotgun metagenomics, differences in mucosal and fecal microbiota in the terminal ileum and colon were noted and linked to metabolic functions.[69] Such differences between luminal and mucosal communities have, indeed, been documented in IBS,[70,71] but their pathophysiological and clinical significance is unclear.
3. Intrinsic variability between subjects in heterogeneous populations, such as IBS, may, in turn, reflect genetic, cultural, socioeconomic, or ethnic variances.
4. The impacts of diet, medications, and other environmental exposures (eg, a gluten-free diet), so commonly instituted by IBS subjects, have been shown to change the microbiome of health adults.[72]
5. Differences in subject selection and in the definition of study populations.
6. Overlap between IBS and other DGBI.
7. The impact of common comorbidities, such as anxiety, depression, or susceptibility to stress, for example, in IBS.[73,74]
8. Early life events, such as antibiotic exposure or traumas, which may predispose to IBS and also impact on the microbiome at a critical time in its evolution.
9. Influence of subtype—diarrhea versus constipation. In 2 large general population studies, Bristol stool form along with various life-style factors was a much greater contributor to interindividual variation in the fecal microbiome than any clinical diagnosis, including IBS, suggesting that bowel function, per se, had a significant impact on microbiome composition.[75,76]
10. The impact of the disorder itself. The paucity of longitudinal studies is especially problematic regarding this issue as there is evidence, from a cross-sectional study, that symptom severity in IBS is linked to specific enterotypes.[77] Interestingly, this signature was identified using machine learning; no differences in microbiota abundance or composition were detectable using conventional

methods, as noted by others.[78] Just as each human subject represents the unique convergence of their genetic make-up and a host of environmental factors, the composition of the microbiota is similarly unique. Despite the uniqueness of the human microbiota for each subject, evidence has been presented to indicate that at a high level of organization, the microbiota of large populations of individuals contains certain similarities, termed as enterotypes.[79] However, there is currently controversy on how enterotypes should be defined, how many there are, whether they are a fixed entity or whether they represent an optimal structure in a given ecosystem.[80,81] Studies also revealed that individual human subjects can switch enterotypes over the longer term[82] and that the *Prevotella* and *Bacteroides* enterotypes, were associated with long-term high carbohydrate and animal protein and fat consumption, respectively.[83] These data emphasize the importance of longitudinal and carefully controlled studies. With the advent of metagenomics and metabolomics and their displacement of 16S based sequencing in the analysis of the human microbiome, the enterotype issue has become somewhat moot as investigators now seek to obtain both a much more detailed identification of microbial populations and their functional and metabolic properties.

So, where are we in the study of microbial populations in IBS?

The Fecal Microbiome in Irritable Bowel Syndrome

Because of the ease of collection, most studies on the gastrointestinal microbiome in IBS have been based on fecal sampling. A Rome Foundation report concluded in 2013 that while some microbial groups, such as *Faecalibacterium prausnitzii* and other potential butyrate producers, as well as *Akkermansia muciniphila*, a mucin degrading bacterium, were typically abundant in healthy controls, several potentially pathogenic groups belonging to the phylum Proteobacteria were more evident in IBS.[84] I have already alluded to evidence that enterotypes enriched in Clostridiales or Prevotella species are linked to symptom severity in IBS.[77] However, in their 2019 meta-analysis, Pittayanon and colleagues emphasized the many shortcomings of available studies and noted that, perhaps as a consequence, results on microbial diversity in IBS were highly variable. Overall, they found that the family Enterobacteriaceae (phylum Proteobacteria), family Lactobacillaceae, and genus Bacteroides were increased in patients with IBS compared with controls, whereas uncultured Clostridiales I, genus Faecalibacterium (including *F prausnitzii*), and genus Bifidobacterium were decreased.[85] More recent studies and an updated meta-analysis have provided supportive findings with respect to an increased abundance of Enterobacteriaceae and decreased abundance of Bifidobacteria and *F prausnitzii*.[86–91] In one of these studies, Plantinga and colleagues detected an interaction between abundance of Bifidobacteria and tryptophan intake in predicting stool character among 115 females with IBS.[87] Kim and colleagues performed a case-control study on 567 IBS patients and 487 healthy individuals from 10 shared data sets that used the same methodology.[90] In the combined data set, α-diversity was reduced in IBS and, though there was considerable variability between studies, 36 species were identified at least once as having a lower abundance in IBS and 6 more abundant. However, bacterial communities between IBS patients and healthy controls were poorly separated[90]; again, illustrating the challenges posed by microbiome analyses in such a heterogeneous disorder.

Multiomics approaches may provide a way forward. In one of the most comprehensive studies to date, Mars and colleagues, in a longitudinal study, integrated data from the gut microbiome, metabolome, host epigenome, and transcriptome with IBS

phenotype and physiology.[40] Their longitudinal approach revealed the shortcomings of cross-sectional studies by demonstrating that differences in taxa abundances between healthy controls and IBS subtypes observed at individual time-points were highly inconsistent and did not overlap with changes observed in averaged data where some separation was evident between IBS subtypes and healthy controls, including a higher abundance of multiple *Streptococcus* spp. Furthermore, they found that the colonic mucosal microbiome was quite different from that in the feces with the former featuring a greater abundance of Proteobacteria in IBS than in the control subjects. Metabolomic data revealed reduced levels of hypoxanthine and a state of purine starvation in IBS, in general, and when combined with mucosal physiologic testing, nicely separated IBS-D (increased tryptophan, tryptamine, and primary bile acids in stool and enhanced mucosal permeability) from IBS-C (decreased short chain fatty acids in stool and biopsy, decreased primary bile acids in stool, and decreased 5-hydroxytryptamine in biopsy).[40]

Using a similar approach, Jacobs and colleagues[92] associated IBS with differential abundance of certain bacteria taxa, changes in metabolites such as tyramine (increased), gentisate, and hydrocinnamate (both decreased) and transcripts related to fructo-oligosaccharide and polyol utilization. They also achieved differentiation between diarrhea-predominant and constipation-predominant IBS with a high degree of accuracy using a classifier incorporating metabolites and gene-normalized transcripts.[92] In another study from the same group, microbiome and metabolome were inked to pathophysiological features of IBS such as visceral hypersensitivity and central perception and processing.[93] Su and colleagues were also able to separate IBS subtypes through bacterial diversity and metabolites but also, and importantly, noted the impact of disease severity, age, psychological comorbidity, and diet.[94] In contrast, Mujagic and colleagues could not separate IBS subtypes based on microbiome-metabolome data but were able to delineate other IBS clusters that linked IBS duration, stress, and diet to certain metabolic pathways including those related to tryptophan.[95]

Other Constituents of the Microbiome

To date, viruses, fungi, and other members of the microbiome have received relatively little attention. Changes in the virome have been described in IBS and appeared independent of IBS subtype or diet and did not covary significantly with the bacteriome.[96] These findings contrast with those of Li and colleagues who, though also noting changes in viral abundance in IBS, found that these covaried with shifts in bacterial abundance.[97]

With regard to the mycobiome, data are also sparse. While it has been hypothesized that certain fungi, and Candida species, in particular, may play a role in the pathogenesis of visceral pain in IBS,[98,99] clinical studies, to date, have failed to identify a mycobiome signature characteristic of IBS.[99,100]

Fecal versus Colonic Mucosal Microbiome

Differences between mucosal and fecal microbiomes were noted in the earlier referenced study by Mars and colleagues,[40] a finding confirmed in other studies.[101–103] Sundin and colleagues, noting a difference in fecal microbial composition between IBS subjects and healthy controls, also found that the mucosal bacterial profile of the sigmoid colon, but not the duodenum, differed between these 2 groups.[48] In another study, the same group noted that fecal microbiota showed covariation with mucosa adherent microbiota.[77] Hou and colleagues[101] and Choo and colleagues[102] both noted distinct differences between the fecal and mucosal microbiota in IBS

and concluded that the latter was more relevant to bowel habits and pathophysiology of IBS.

SUMMARY

So, what do we make of all this data? The inconsistent nature of microbiome data generated from 16S sequencing illustrates the impact of the many challenges previously described in this article. Many environmental and personal factors impact microbiome composition and function and have not always been controlled for in microbiome studies. Among these, diet is of overarching importance and includes the effects of dietary modifications employed to treat IBS, such as the low fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) diet, on the microbiome. Symptom severity and activity are also relevant to changes in microbiome, metabolome, and meta-transcriptome,[40,77] emphasizing the critical importance of longitudinal studies. An overreliance on fecal samples may have led us to miss valuable information detectable from an examination of the juxtamucosal microbiome. With regard to the virome and the mycobiome, data are very limited, and this area clearly merits further study.

From multiomics studies new information is beginning to emerge, some predictable such as the changes in bile acids and short chain fatty acids[40]; some novel, such as changes in purine and tryptophan metabolism.[40] These studies offer insights into the pathophysiology of IBS, could lead to the identification of new IBS subgroups and might even offer help in diagnosis. How can the microbiome promote symptom alleviation in IBS? Given all that has been said about the heterogeneity of the syndrome and the profusion of confounding factors, one hopes that studies involving well-phenotyped subjects (not just for stool form but also for psychological burden and dominant symptoms, for example) and well controlled for diet and therapy will identify signatures predictive of response to effective microbiome-modulating therapies.

CLINICS CARE POINTS

- Enteric infections can lead to the development of IBS.
- The status of small intestinal bacterial overgrowth in IBS remains uncertain and awaits the defintion of the small intestinal microbiome in health and IBS.
- Many factors compilcate the interpretation of colonic and fecal microbiome studies in IBS.
- A microbiome signal characteristic of IBS has yet to be defined though some aspects of IBS might be linked to specific microbiome signatures.
- Other 'omics, such as metabolomics may provide imporatnt insights in to IBS pathophysiology.

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