

REVIEW

The Structure and Function of the Human Small Intestinal Microbiota: Current Understanding and Future Directions

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SUMMARY

There is limited information about the small intestinal microbiota, an ecosystem that is relevant to many physiologic mechanisms and pathologic states. Here, we highlight human and animal studies to advance understanding of microbe-influenced human conditions, and the fundamental distinctions of this population relative to the large intestine.

Despite growing literature characterizing the fecal microbiome and its association with health and disease, few studies have analyzed the microbiome of the small intestine. Here, we examine what is known about the human small intestinal microbiota in terms of community structure and functional properties. We examine temporal dynamics of select bacterial populations in the small intestine, and the effects of dietary carbohydrates and fats on shaping these populations. We then evaluate dysbiosis in the small intestine in several human disease models, including small intestinal bacterial overgrowth, short-bowel syndrome, pouchitis, environmental enteric dysfunction, and irritable bowel syndrome. What is clear is that the bacterial biology, and mechanisms of bacteria-induced pathophysiology, are enormously broad and elegant in the small intestine. Studying the small intestinal microbiota is challenged by rapidly fluctuating environmental conditions in these intestinal segments, as well as the complexity of sample collection and bioinformatic analysis. Because the functionality of the digestive tract is determined primarily by the small intestine, efforts must be made to better characterize this unique and important microbial ecosystem. (*Cell Mol Gastroenterol Hepatol* 2020;9:33–45; <https://doi.org/10.1016/j.jcmgh.2019.07.006>)

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The communities of microorganisms in the human digestive tract are a complex ecosystem that is both essential for health and also a potential driver of a variety of pathologies. The adult human intestine is colonized by more than 1000 microbial species encompassing all domains of life: archaea, bacteria, and eukarya. The large intestine harbors approximately 10^{10} – 10^{11} colony-forming units (CFU)/mL, the composition and dynamics of which have been described previously.^{1–3} The properties of the

microbiota in the human small intestine are less well characterized, primarily because of challenges in sampling this segment of the digestive tract.^{4,5} Studying the small intestine ecosystem is principally relevant to digestive health, because the duodenum and jejunum are tasked with facilitating the majority of nutrient assimilation and absorption.⁶ In addition, there is significant contact between food substrate and commensal bacteria in the small intestine, creating an environment rich in microbe–microbe and host–microbe interactions.⁴ Studying these concepts is challenged by rapidly fluctuating environmental conditions in these intestinal segments, as well as the complexity of sample collection and bioinformatic analysis.⁷ Here, we examine what is known about the human small intestinal microbiota in terms of community structure and functional properties, methodologic challenges, and the roles of this community in select human pathologic conditions.

Methodologic Challenges in Studying the Small Intestinal Microbiota

A distinguishing feature of the small intestine compared with the colon is its relative inaccessibility, which poses challenges to sampling and experimental design. Although fecal samples most commonly are collected in studies of the gut microbiota, stool more accurately represents the distal portions of the gut,⁵ leaving the small intestinal microbiota communities hidden from view. Studies of the human small intestinal microbiota have involved invasive sampling procedures including esophagoduodenogastroscopy and nasoduodenal catheters, while other studies have sampled ileal mucosa obtained during colonoscopy, intestinal resection, small-bowel transplantation, or from sudden death victims.^{8–13} These methodologies are subject to contamination from the oropharyngeal cavity or colon, and also limit the

Abbreviations used in this paper: BA, bile acid; CFU, colony-forming units; EED, environmental enteric dysfunction; FAP, familial adenomatous polyposis; FXR, farnesoid X receptor; GF, germ-free; HF, high-fat; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IPAA, ileal pouch–anal anastomosis; PN, parenteral nutrition; SBS, short-bowel syndrome; SIBO, small intestinal bacterial overgrowth; UC, ulcerative colitis.



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ability to study microbial dynamics as a function of time or environmental change (eg, diet). Some studies have enrolled participants with ileostomies, which affords longitudinal effluent sampling directly from the small intestine.^{14–18} Although this may be methodologically advantageous, it is important to recognize that ostomy samples are exposed to the skin and external environment, which may impact the microbial community.¹² An additional methodologic challenge of microbiome investigations is moving beyond correlations and associations, toward better pinpointing microbe–phenotype relationships and causality.¹⁹ Thus, animal models of germ-free (GF), gnotobiotic, and conventionalized mice continue to be valuable for mechanistic exploration, although major differences to human beings in terms of intestinal size, metabolic rate, dietary habits, and spatiotemporal microbial structures need to be considered carefully when extrapolating data.²⁰ The term *dysbiosis* is used pervasively in microbiota literature to refer to microbial imbalance, and serves as a broad communication tool without clear establishment of cause and effect.²¹ The challenge moving forward is to establish when and how dysbiosis contributes to a disease state as opposed to its presence alone.

The Diversity and Temporal Dynamics of the Small Intestinal Microbiota

The small intestine is a harsh environment for microbial life owing to short transit time, the influx of digestive enzymes and bile, and intermittent food substrate delivery. As a result, the bacterial populations in this region of the intestinal tract have a lower biomass, are less diverse, but are more dynamic, given the need to respond to rapidly changing luminal conditions. Generally speaking, bacterial populations increase from approximately 10^{4-5} CFU/mL in the duodenum to 10^{7-8} CFU/mL in the distal ileum, where transit slows (Figure 1).¹³ In addition, the proportion of gram-positive to gram-negative, as well as facultative anaerobic and strict anaerobic, species increases from proximal to distal segments of the small intestine and colon.^{13,22} These changes are thought to be secondary, in part, to oxygen use by proximal aerobic and facultative anaerobic communities.¹³ Bacterial genera commonly found in the small intestine include *Lactobacillus*, *Clostridium*, *Staphylococcus*, *Streptococcus*, and *Bacteroides*, among others,^{9,11,13} but taxonomic classification has been inconsistent across studies^{4,9,11,13,17,18,22–27} owing to differences in sample collection and analytic methodologies (Figure 2).

A major concept that has been shown across studies is that the small intestinal microbiota is phylogenetically less diverse than the colon, but more dynamic. Booiijink et al¹⁵ highlighted this concept in their study of 7 patients with inflammatory bowel disease (IBD), all of whom had ileostomies. There, the ileal effluent had a higher relative abundance of species within the orders *Lactobacillales* and *Clostridiales*, mainly *Streptococcus bovis*-related species, and the *Veillonella* group.¹⁵ There were significant interindividual differences, and intraindividual temporal fluxes, between morning and afternoon profiles over a period of 9–28

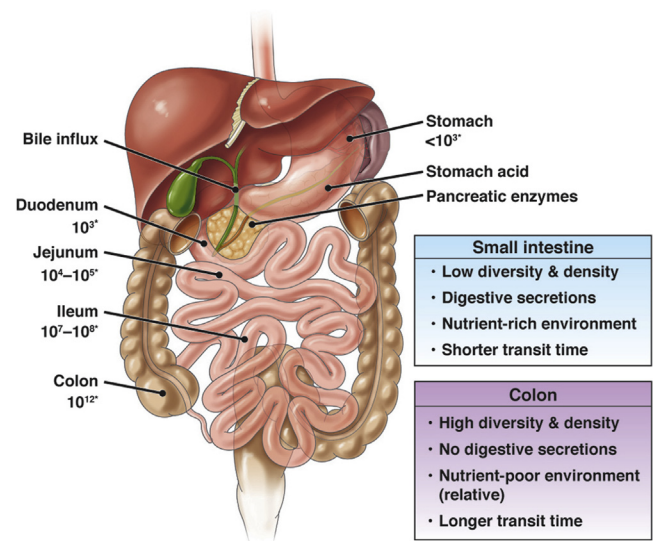


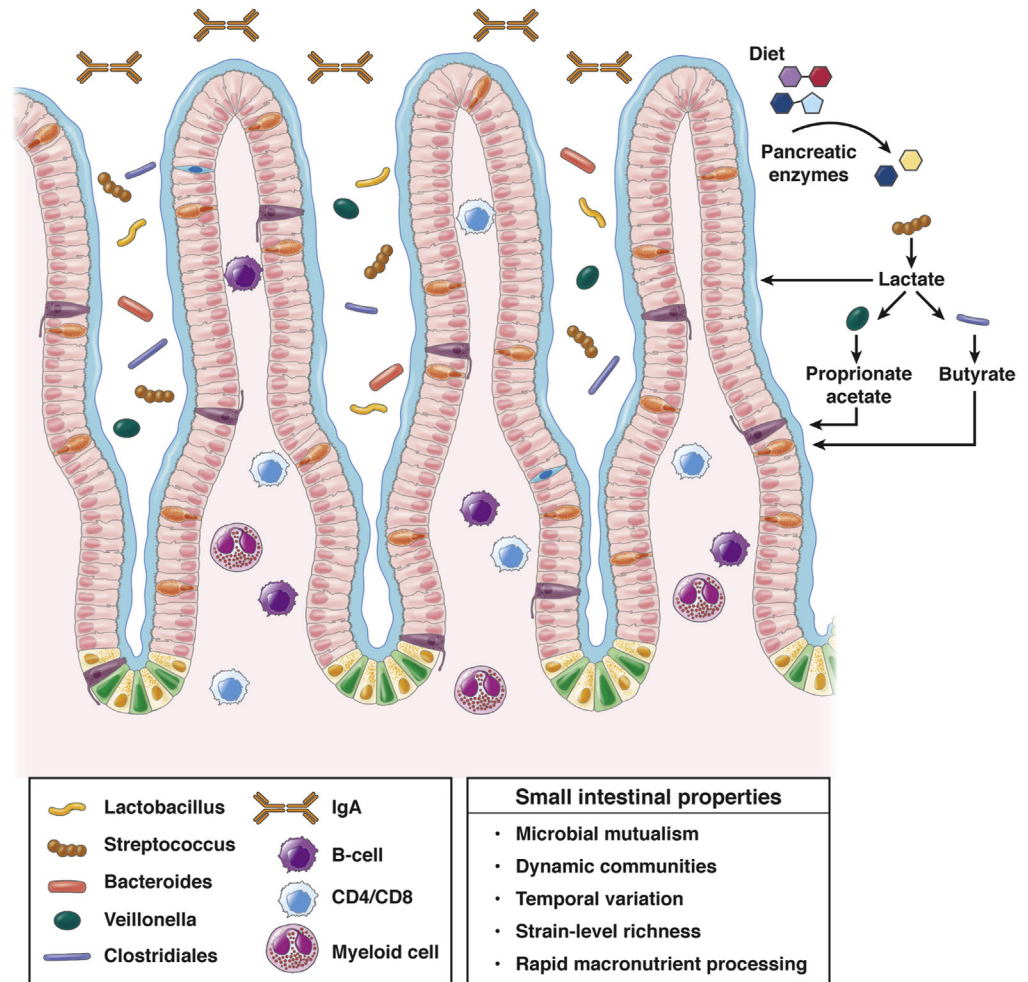
Figure 1. Overview of bacterial colony density throughout the digestive tract, factors from the proximal tract that shape small intestinal communities, and distinguishing characteristics of the small intestine and colon.

days,¹⁵ a notion that has been corroborated over a much longer study period.¹⁸ A separate study looking specifically at *Streptococcus* and *Veillonella* species from ileostomies highlighted that there is incredible strain-level richness in the small intestine.¹⁷ There, 16S ribosomal RNA gene sequencing showed a total of 160 *Streptococcus* and 37 *Veillonella* isolates, with temporal variance in 7 predominant isolates within a 72-hour time frame. The theme of temporal variation in the small intestinal microbiota is a stark contrast to the relatively stable composition in the colon,^{15,17,18,28} and dietary influences may drive some of these findings.

Dietary Influences on Community Structures and Functions

Carbohydrates and the Small Intestinal Microbiota

A major contributor to the luminal environment is the host diet, and studies have examined the effects of isolated macronutrients on the structure of small intestinal microbial communities and resulting metabolic profiles. Carbohydrate fermentation is a core function of the gut microbiota. Zoetendal et al¹⁸ collected ileostomy effluent samples to show that the small intestinal metagenome, compared with the fecal metagenome, is significantly more enriched with genes related to carbohydrate metabolism. Processes such as sugar phosphotransferase systems, the pentose phosphate pathway, lactate and propionate fermentation, as well as cofactors such as cobalamin and biotin, were encoded across many taxa from ileal effluent, and in particular *Streptococcus*, arguing that carbohydrate metabolism is a central function of the collective small intestinal microbiota.¹⁸ Metatranscriptomic analysis showed that the earlier-mentioned metabolic processes are highly active, and that the small intestinal microbiota



adapt rapidly to fluctuating nutrient availability in the lumen, rapidly metabolizing simple carbohydrates for community maintenance.¹⁸ This contrasts with colon communities, which are more equipped to degrade complex carbohydrates.²⁹ *Streptococci* are enriched with genes for energy generation, and are suggested to make a considerable contribution to primary digestion of food components in the small bowel,¹⁸ with fermentation products that support the growth of secondary fermenters (eg, *Veillonella*, *Clostridium*) (Figure 2). Indeed, cohabitation of *Streptococcus* and *Veillonella* occurs not only in the intestine, but also in the stomach, esophagus, throat, and oral cavity,^{30,31} and is likely attributed to their metabolic interaction surrounding lactic acid production and utilization, respectively.³²

Dietary Fat and the Small Intestinal Microbiota

Lipid digestion and absorption are complex physiological processes that are central to the duodenum and jejunum.⁶ GF mice have increased fecal lipid levels compared with mice in conventional housing,³³ positing that the microbiota modulates lipid digestive physiology. Furthermore, the

small intestinal microbiota differ when comparing mice on low-fat and high-fat (HF) diets.³⁴ A HF diet induces an abundance of *Clostridia*, while decreasing *Bifidobacteria* and *Bacteroides*, creating a microbial genetic profile with an enhanced capacity for inducing genes involved in small intestine epithelial lipid transport and pancreatic cholecystokinin signaling.³⁴ Indeed, when a HF diet microbiota was transplanted into GF mice, lipid absorption improved.³⁴ We know from fecal-based human studies that diet can alter the colonic microbiota and metabolites within 48 hours, as well as lead to long-term reductions in diversity and taxonomic changes such as increases in Firmicutes and Proteobacteria.^{35–37} Future investigations should consider the small intestinal microbiota's response to factors such as fat saturation status and varying fatty acid composition, and dietary intervention studies are needed.

Of particular relevance to studying microbial–fat digestion interplay is the influence of bile acids (BAs) both on digestive physiology and community structure (Table 1). Primary BAs are synthesized in the liver, secreted into the small intestine, and are central to emulsification and absorption of dietary lipids and fat-soluble vitamins.^{38,39} They also affect bacterial growth, particularly gram-positive

Table 1. Small Intestinal Microbiota, Select Roles, and Physiologic Effects

Nutrient	Mechanism
Carbohydrate digestion	Degradation and fermentation of diet-derived simple carbohydrates into organic acids, aldehydes, alcohols, and gases Impaired brush-border disaccharidase activity Hydrogen sulfide and hydrogen gas contribute to intestinal motility regulation through effects on smooth muscle
Fat digestion and bile acid physiology	Bile acid deconjugation, decreased bile acid pool for fat solubilization lead to steatorrhea Bile acid (eg, lithocholic acid) may directly inhibit absorption, leading to steatorrhea Induce intestinal peristalsis and contractions mediated by Takeda G-protein coupled Receptor 5 on enteric neurons and enteroendocrine cells (deoxycholic acid) Secondary bile acid pools stimulate chloride and water secretion
Micronutrient stores	Vitamin K stores may be increased owing to bacterial synthesis Direct bacterial consumption for vitamin B12 and modification for use as own cofactor Anaerobe-induced inhibition of vitamin B12 absorption in terminal ileum Fat-soluble vitamin deficiency from deconjugated bile acids, decreased fat absorption

colonies, through oxidative stress and DNA damage,⁴⁰ and exert wide-ranging physiologic effects through activation of the nuclear hormone receptor farnesoid X receptor (FXR) and the G-protein-coupled receptor Takeda G-protein coupled Receptor 5.⁴¹ Suppression of bile acid synthesis via obeticholic acid (a semisynthetic primary bile acid and activator of FXR) causes induction of small intestinal gram-positive bacteria in human fecal samples.³⁸ As part of the enterohepatic circulation, primary BAs are conjugated to glycine or taurine, and are reabsorbed in the distal ileum. Bacteria in the ileum express bile salt hydrolases, which induce deconjugation of primary BAs, and subsequent conversion to secondary BAs through bacteria-mediated 7- α -dihydroxylation.⁴⁰ Secondary BAs in turn are mediators of microbial–host communication, in part through regulation of the FXR pathway.⁴² GF mice have increased conjugated BAs, such as tauro- β -muricholic acid, compared with conventionalized mice,^{42,43} which antagonizes intestinal FXR. Tempol is an antioxidant that preferentially reduces *Lactobacillus* and its bile salt hydrolases, causing accumulation of tauro- β -muricholic acid, and subsequent FXR antagonism.⁴⁴ Separately, there is evidence that BAs can contribute to diarrhea and inflammation. A high milk-fat diet³⁴ increased taurine-conjugated BAs, facilitated an abundance of sulfite-reducing *Bilophila wadsworthia*, which in turn was correlated with colitis in genetically susceptible interleukin 10 knockout mice.⁴⁵ Because sulfate-reducing organisms preferentially transport their nutrients from sites of inflammation, they have relevance in IBD and are found in abundance in mucosal biopsy specimens from patients with ileal Crohn's disease.^{46,47} Taken together, these studies are beginning to show that small intestinal microbial communities depend on the capacity to quickly metabolize temporarily available macronutrients, and the resulting metabolites are integrated into an enormously complex network of microbe–microbe and microbe–host interactions. Certainly, more mechanistic investigation is needed, and there are clues from human disease processes that can serve as models to help guide future research.

Micronutrients and the Small Intestinal Microbiota

Beyond their roles in the digestive physiology of dietary macronutrients, the small intestinal microbiota also contributes to synthesis and assimilation of several important micronutrients (Table 1). Proper fat absorption is crucial for maintaining fat-soluble vitamin stores, and all but vitamin K are absorbed via passive diffusion in the small intestine.^{48,49} Although human vitamin K1 (phytomenadione) stores are derived primarily from dietary plant sources, the majority of vitamin K2 (menaquinone) is generated by intestinal bacterial biosynthesis.⁵⁰ *Veillonella*, *Enterobacteriaceae*, *Bacteroides*, and *Prevotella* all have been shown to synthesize this nutrient. Small intestinal bacterial overgrowth (SIBO), a condition discussed later in this review, is associated with impaired vitamin K metabolism in human beings.^{51,52} Vitamin B12, whose digestive physiology is intimately linked to the small intestine, also is impacted by bacterial biology. Facultative gram-negative aerobes and anaerobes are capable of competitively using cobalamin as a cofactor for their own metabolic processes.⁵³ Thus, cobalamin deficiency is a complication of SIBO, likely resulting from competition between bacterial metabolism and host absorption.⁵⁴ Indeed, in vitro models have shown that members of the genus *Bacteroides* outcompete intrinsic factor for binding to cobalamin, interfering with absorption in vivo.⁵⁵ Folate levels, by comparison, may be increased in SIBO as a result of bacterial biosynthesis.⁵⁴ Iron, thiamine, and nicotinamide deficiencies also have been described in SIBO, although the mechanisms are not fully elucidated.⁵⁶

Disease Models of Dysbiosis in the Small Intestine

Although SIBO has been investigated for decades, it remains diagnostically challenging owing to difficulty characterizing and analyzing the small intestinal microbiota. SIBO is often a consequence of gut stasis, and has been studied in the context of anatomic abnormalities in the small intestine including diverticulae,⁵⁷ surgically created blind loops,⁵⁸

strictures,⁵⁹ and also dysmotility.⁶⁰ In these disorders, there is ineffective food clearance, enhanced bacterial contact with food substrate, and subsequent bacterial colony expansion.⁶¹ Biochemically, bacterial fermentation of carbohydrate sources leads to production of organic acids, aldehydes, alcohols, and gases.^{62–64} When excessive fermentation occurs in the small intestine, metabolic byproducts contribute to bloating, nausea, abdominal pain, distention, and acidic stools. Rarely, encephalopathy from D-lactic acidosis^{65,66} is a metabolic complication of SIBO that results from excessive fermentation by *Lactobacilli* species, *Enterococci*, and *Streptococci*, and, interestingly, has been described only in patients with short-bowel syndrome (SBS).^{67,68} Typically, primary bile salts assist with fat absorption before deconjugation and reabsorption in the ileum.³⁹ With bacterial overgrowth, however, steatorrhea and fat-soluble vitamin deficiency can result from premature bacterial deconjugation of primary bile salts.^{69,70}

At present, the most commonly used tests to diagnose SIBO in clinical practice are hydrogen and methane breath tests, and small-bowel aspirate for culture. Both of these modalities have significant diagnostic and practical limitations.⁷¹ In the human gut, the majority of methanogenic archaea, classically *Methanobrevibacter smithii*, deplete hydrogen in the generation of methane.⁷² Through scavenging hydrogen produced by neighboring microbes, termed the *sink effect*, methanogenic bacteria allow increased polysaccharide fermentation by neighboring microbes.⁷³ This normal physiology predominates in the colon, but also can be altered in SIBO, leading to depleted methanogenic species, and subsequently positive hydrogen breath tests.⁷² However, both sensitivity and specificity are variable, and, as a consequence, the symptomatic response of a trial of antibiotics often is substituted for objective testing in clinical practice. Despite the risk for contamination and its invasive nature, small-bowel aspiration for culture has the advantage of potentially identifying the organisms involved in SIBO, and the antimicrobial sensitivities thereof. A wide variety of oropharyngeal and colonic commensal bacteria have predominated duodenal and proximal jejunal cultures in patients with SIBO-induced diarrhea and malabsorption, including *Streptococcus*, *Escherichia*, *Staphylococcus*, *Klebsiella*, *Proteus*, *Lactobacillus*, *Bacteroides*, *Clostridium*, *Veillonella*, *Fusobacterium*, and *Peptostreptococcus*, among others,^{23,74} meaning that SIBO, as a heterogeneous entity, is unlikely to be caused by a single bacterial strain. A deeper understanding of SIBO is needed to better understand the host–microbe relationships in the small intestine, and to develop improved diagnostic and treatment modalities.

Short-Bowel Syndrome

SBS occurs when a significant amount of small intestine is surgically removed, resulting in malabsorption that disrupts protein–energy, fluid, electrolyte, and micronutrient balances.⁷⁵ Patients with SBS have disrupted microbiota related not only to the anatomic change, but superimposed parenteral nutrition (PN), variable enteral intake, and

potentially recurrent antibiotic exposure. Small studies analyzing fecal samples have shown that the diversity of the colonic bacteria is reduced, with a higher proportion of the proinflammatory *Proteobacteria* phylum.^{76–78} Interestingly, longer bowel length or increased enteral nutrition over time reduced the amount of *Proteobacteria*.⁷⁷ Patients with SBS have a higher abundance of *Lactobacillus* in fecal samples, bacteria that are efficient fermenters, but also may induce encephalopathy and acidosis through D-lactate production.^{78–80} When feces from patients with SBS are transplanted into GF rats, the SBS microbiota stimulate colonocyte proliferation and gut hormone production.⁸¹ However, the excess D-lactate production was not transferred, indicating that the host small intestine may be protective against this systemic acidosis.⁸¹ In addition to disruption of the colonic bacteria in patients with SBS, small intestinal bacteria also is disrupted such that patients with SBS have a high incidence of SIBO as diagnosed by a glucose breath test⁸² and duodenal aspirate,^{83,84} where gas production can lead to severe abdominal distension, and in turn limit the ability to tolerate food. One study showed that 70% of children who had refractory bloating, diarrhea, or emesis had duodenal aspirates consistent with SIBO, with *Escherichia coli*, *Klebsiella*, *Streptococcus viridans*, and *Enterococcus* being the most common organisms.⁸³ Although PN can be life-saving in this population, children with SBS who need PN, particularly those with SIBO, have a high incidence of gram-negative and enteric bacteremia⁸² suspected to result from mucosal atrophy, barrier impairment, and translocation of bacteria or proinflammatory compounds.^{82,85} Many *Proteobacteria* produce lipopolysaccharide, which can induce a sepsis picture and liver damage through Toll-like receptor pathway activation.⁸⁶ *Proteobacteria* were associated with prolonged PN and hepatitis, and *Lactobacilli* were associated with advanced steatosis and fibrosis, mostly after weaning off PN.⁸⁷ This may suggest that steatosis begins during PN in response to, for example, proinflammatory lipopolysaccharide produced by *Proteobacteria*, and progresses after weaning off PN because *Lactobacilli* become dominant and affect lipid metabolism through altered BA signaling.⁸⁷ Ongoing insult may lead to the need for liver and/or intestinal transplantation, an important cause of significant morbidity and mortality in SBS patients.⁸⁸ Indeed, more investigation into the small bowel specifically is needed to develop improved diagnostics and therapeutic targets.

Pouchitis

The etiology of IBD is a complex interplay of factors including genetic susceptibility, interaction of mucosal immunity with environmental triggers, and the intestinal microbiota.⁸⁹ An alternative to an ileostomy for patients with IBD whose colon has been removed is an ileal pouch–anal anastomosis (IPAA), in which an ileal reservoir, or pouch, is surgically created and anastomosed to the anal canal. This surgery also may be indicated for patients with familial adenomatous polyposis (FAP), in whom a colectomy often is performed to remove innumerable precancerous or

transformed polyps.⁹⁰ Inflammation of the pouch, termed *pouchitis*, may manifest as tenesmus, diarrhea, and blood per rectum,^{5,91–93} and frequently is treated with antibiotics. Interestingly, pouchitis occurs in approximately half of patients with IBD pouches, but seldom in FAP patients,^{91,94} suspected to be owing in part to a higher basal epithelial turnover rate in FAP.⁹⁵ In patients with multiple-stage IPAA surgery, biopsy specimens upstream from the ileostomy at the time of stoma closure harbor predominantly facultative anaerobes (eg, *Lactobacilli*, *Enterococci*, and coliforms), a paucity of sulfate-reducing bacteria, and low levels of *Clostridium perfringens*.⁹⁶ After ileostomy closure, the bacterial biomass increases in the ileal pouch, and populations shift with decreased facultative anaerobes and increased obligate anaerobes, sulfate-reducing bacteria, and *Clostridia* species,^{96–98} which is much more prominent in ulcerative colitis (UC) pouches compared with FAP. Mucosal adaptation occurs in maturing ileal pouches, and the presence of feces has been associated with colonic metaplasia and transformed mucin glycosylation.⁹⁹ These changes do not happen in ileostomies before IPAA,^{100,101} and also are more prominent in pouches from UC patients compared with FAP patients,⁹⁵ arguing that fecal stasis may be a contributing factor in the metaplasia process. Sulfomucin provides a metabolic substrate for sulfate-reducing bacteria such as *Bacteroides fragilis*,^{102–104} which promote colonization and expansion of these bacteria, and explains the high prevalence of sulfate-reducing bacteria in UC, compared with minimal or no colonization in FAP pouches.^{95,96,105} What has yet to be well characterized are the microbiota differences between UC and FAP ileostomies, before IPAA occurs, which may help elucidate why metaplasia and pouchitis occur to a greater extent in UC patients.

Environmental Enteric Dysfunction

Childhood malnutrition is a global health challenge, and there are new insights about the roles of microbiota maturation and enteropathogen burden as perpetuators of malnutrition. Malnourished children have an impaired microbiota maturation index, and stool transplantation from malnourished children into GF mice transmit an impaired growth phenotype.¹⁰⁶ Adding routine antibiotic agents to nutritional interventions has been shown to decrease mortality in children with uncomplicated severe acute malnutrition,¹⁰⁷ providing additional evidence for the relevance of studying microbial-based interventions in this condition. Environmental enteric dysfunction (EED) is the intersection of dietary macronutrient insufficiency with small intestinal dysfunction and is a significant contributor to global malnutrition in children.^{108–110} EED is characterized by increased inflammatory markers,^{111,112} increased markers of small intestinal permeability, and bacterial protein translocation.^{113–116} Dietary intervention alone is not fully effective in treating malnutrition in patients with EED,¹¹⁷ and a disrupted resident small intestinal microbiota is hypothesized to play a key role in the pathogenesis of EED.¹¹⁸ Enteropathogens commonly isolated in fecal samples from

stunted children, including *Campylobacter* species, *Cryptosporidium*, *E coli* pathotypes, and *Giardia*, normally reside in the small intestine^{119–121} and have been associated with EED. Furthermore, SIBO as diagnosed by a breath test is associated with malnutrition and poor sanitation.^{122–124} Although sampling the small intestinal microbiota in patients with EED has not been reported, there is evidence from mouse models that protein malnutrition predisposes the small intestine to persistent pathogen colonization and mucosal injury.^{125,126}

It already is known that malnutrition itself can significantly alter the microbiome in the duodenum, with a shift toward *Bacteroidetes* and *Proteobacteria*, and changes in bile acid and vitamin pools.¹²⁶ To recapitulate the small intestinal villus blunting and inflammation characteristic of EED, infection must co-occur with malnutrition. Several models of EED with dietary restrictions and concomitant enteric pathogen exposure have been detailed, including *Giardia*,¹²⁷ *Cryptosporidium*,¹²¹ *Enterococci*,¹²⁸ and a mixture of *E coli* and *Bacteroidales*.¹²⁶ The dysbiosis induced by malnutrition, coupled with exposure to these specific microbes, makes the host more susceptible to adherent bacteria¹²⁶ and allows pathogens to trigger an immune response that is ongoing, even after the pathogen is cleared. In the setting of protein malnutrition, even a small inoculum of *Cryptosporidium* triggered increases in chemokine ligand 5, interferon γ , and B- and T-cell infiltration into the lamina propria, an effect that was not seen in fully fed mice.¹²⁹ Taken together, the evidence suggests that in EED, protein malnutrition provides a platform for disrupted resident microbiota and propagation of intestinal pathogen colonization and small intestine injury.

Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is a clinical diagnosis characterized by a change in stool characteristics and associated abdominal discomfort, and has long been speculated to be associated with changes in the gut microbiome.¹³⁰ Although the reported prevalence of SIBO in IBS is variable based on diagnostic modality, meta-analyses have shown that more than one third of IBS patients have SIBO.¹³¹ Furthermore, antibiotic treatment including rifaximin¹³² and dietary interventions including low fermentable oligo-, di-, monosaccharides and polyols are beneficial in the treatment of IBS, providing further evidence for a microbial basis. Changes in the populations of *Bifidobacteria*,¹³³ *Prevotellaceae*,¹³⁴ *Escherichia*, *Shigella*, *Aeromonas*, *Acinetobacter*, *Citrobacter*, and *Microvirgula*¹³⁵ in the small intestine are associated with IBS, as well as a decrease in α diversity and an increase in the ratio of Firmicutes to *Bacteroidetes*.¹³⁶ *Faecalibacterium* is most abundant in both the duodenum and rectum of patients with the diarrhea type of IBS and is associated with clinical symptoms.¹³⁷ GF mice colonized with the stool of patients with the diarrhea type of IBS showed faster intestinal transit, increased colonic permeability, and increased CD3+ T lymphocytes compared with mice colonized by stool from healthy controls.¹³⁸

In addition, microbially mediated effects on small and large intestinal secretion in IBS may be linked with BA metabolism through deconjugation in the small bowel.¹³⁹ Deoxycholic acid, a secondary BA, has been shown to induce intestinal peristalsis and contractions mediated by Takeda G-protein coupled Receptor 5 on enteric neurons and enteroendocrine cells,¹⁴⁰ and also stimulate chloride and water secretion.^{141,142} There are other lines of evidence that microbial metabolites, such as hydrogen sulfide,¹⁴³ tryptamine,¹⁴⁴ and hydrogen gas,¹⁴⁵ contribute to intestinal motility regulation through their effects on smooth muscle. Given the heterogeneous nature of the disease with multiple putative mechanisms, it will be important moving forward to phenotype patients based on the underlying physiological alterations to develop targeted approaches.

Conclusions

Despite increasing literature characterizing the fecal microbiome and its association with health and disease, few studies have analyzed the microbiome of the small intestine. The immense surface area, an oxygenated environment, the presence of pancreatic and biliary secretions, rapid motility, antimicrobial peptides produced by Paneth cells, and the proximity to ingested nutrients all are factors that differentiate the small intestinal luminal environment from that of the colon, thus leading to a distinctly different composition. Because the functionality of the digestive tract is determined primarily by the small intestine, efforts must be made to characterize the small intestine microbiome, which is central to understanding normal human physiologic responses to diet and nutrient absorption, the development of the mucosal immune system, bile acid biology, and a vast range of pathologic conditions. The effectiveness of antibiotic treatment in diseases such as small intestinal bacterial overgrowth, EED, pouchitis, and IBS provide clear evidence that dysregulation of the small intestinal microbiota plays a fundamentally important role in disease pathogenesis. Technological advances, such as ingested smart capsules, indwelling catheters, as well as animal model systems are needed to gather small intestinal biospecimens, which would facilitate the characterization of small intestinal microbiota dynamics to diet and other perturbations. These samples then would be analyzed using the influx of advanced sequencing and deep metabolomics profiling technologies that have allowed a larger window into the elegant and enormously complex human gut ecosystem. The identification of specific genes and metabolites, their actions, and host targets will in turn allow for novel microbial-based interventions (eg, to promote effective dietary macronutrient and micronutrient processing), genetically modified strains as bacteriotherapy, targeted antibiotic therapy, and functional foods to modulate the small intestine bacteria for specific individual needs.

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Conflicts of interest

The authors disclose no conflicts.