The gut microbiome in patients with intestinal failure: current evidence and implications for clinical practice

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ABSTRACT

Intestinal failure (IF) is the reduction of gut function or mass below a minimum needed to absorb nutrients and fluids, such that patients are dependent on parenteral nutrition (PN). Patients with IF have an altered gut microbiome. Our aim was to review and evaluate the current evidence on gut microbiome and its metabolic activity as well as its association with disease characteristics in adults and children with IF. We performed a PubMed literature search for articles published after 2000 using the following terms: intestinal failure, microbiome, microbiota, short-chain fatty acids, short bowel syndrome and PN. Literature search was restricted to human studies only. The gut microbiome diversity is remarkably reduced, and community structure is altered with a noticeable overabundance of Proteobacteria, especially the Enterobacteriaceae family. A substantial increase in Lactobacillus level is often reported in patients with IF. Gut microbiome characteristics have been associated with poor growth, liver disease, D-lactic acidosis, and duration of intestinal adaptation. Differences in microbiome characteristics have been found between patients receiving PN and those whose guts have adapted and have been weaned off PN. Future research with prospective sample collection should explore the value of the gut microbiome as a biomarker to guide clinical practice and as a modifiable therapeutic target to optimize outcomes of patients with IF.

INTRODUCTION

In the first part of this review, we summarize the primary literature focusing at the gut microbiome characteristics and its association with disease characteristics in patients with intestinal failure (IF). In the second part, we discuss future perspectives on the role of the gut microbiome in the management of patients with IF, including its potential use as a biomarker of intestinal adaptation, prediction of clinical outcomes, and as a therapeutic target.

Intestinal failure

Intestinal failure is defined as the critical reduction of functional gut mass below the minimum needed to absorb nutrients and fluids, such that intravenous supplementation with parenteral nutrition (PN) is required to maintain health and/or growth.[1,2] The intestine is either too short, as a consequence of surgical resection or congenital conditions leading to short bowel syndrome (SBS), or dysfunctional despite adequate length. Symptoms of IF vary from abdominal pain, diarrhea, vomiting, and abdominal distension to dehydration and malnutrition. Patients with SBS may undergo intestinal adaptation, where the remaining small intestine undergoes structural and functional changes to increase its absorptive capacity.[3] This process may eventually allow patients to wean off PN and become fully dependent on enteral and oral feeding.

Human microbiome

It is estimated that the human gastrointestinal tract contains 10^{14} bacteria.[4,5] These gastrointestinal tract-associated microbes are collectively referred to as the gut microbiome. Previous studies have detected bacteria prenatally in the placenta, amniotic fluid, and also in the meconium of newborns.[6-8] Rapid colonization of the gastrointestinal tract starts immediately after birth with its immediate composition depending on gestational age, mode of delivery, and feeding.[9,10] Formula-fed infants tend to have more Bacteroidetes and fewer Actinobacteria and Firmicutes than breast-fed ones.[11]

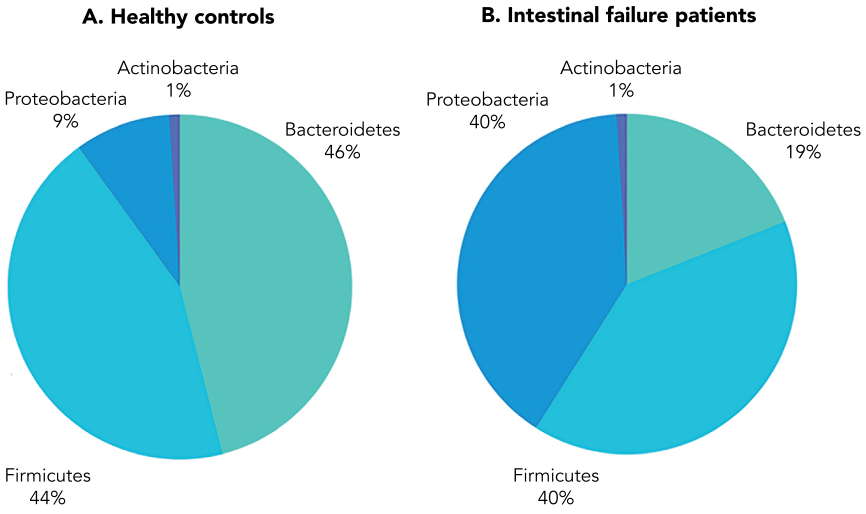
During the first years of life, the gut is gradually colonized, with genetics, environmental factors, diet, and the development of the immune system determining the large extent of compositional variation among individuals.[12-14] The gut microbiome becomes relatively stable in adulthood, with its intraindividual variation being lower than the differences seen between different subjects.[14] Bacteria belonging to Firmicutes and Bacteroidetes phyla dominate the gut and, to a lesser extent, species from Verrucomicrobia, Proteobacteria, and Actinobacteria (**Figure 1**).[15,16]

The gut microbiome is important for several functions such as fermentation and absorption of nutrients in the colon, development of the immune system, and intestinal mucosal

growth and integrity.[17,18] There is growing evidence that certain groups of bacteria such as Clostridia are important for normal intestinal function and protection against intestinal diseases, whereas other proinflammatory bacteria, specifically certain species belonging to Enterobacteriaceae, are harmful.[19-21]

The metabolic functional potential of the microbiome is enormous. Short-chain fatty acids (SCFA) are perhaps the most important bacterial metabolites and end-products of fermentation of nondigestible dietary carbohydrates (i.e. fiber) by anaerobic bacteria. Acetate, propionate and butyrate present 90-95% of the SCFAs produced in the colon.[22,23] Although fiber is the main contributor, proteins, glycoproteins, and peptides from the host's diet and intestinal cell turnover can also constitute fermentation substrate.[24] The colon absorbs >95% of SCFAs[25], contributing to an estimate of 5-10% of the human energy requirements.[26] Moreover, they stimulate vascular flow and motility, increase sodium absorption, affect cell proliferation and differentiation, and promote apoptosis of carcinogenic cells.[22,27,28] Not all bacteria produce the same SCFAs and their molar concentration and proportional ratio in the colon depends also on the type and composition of fermentable carbohydrate.[29]

Figure 1. Pie charts displaying the abundance of major bacterial phyla in patients with intestinal failure and healthy controls



Legend: Average proportions of each phylum were calculated from studies reporting results both in healthy controls and patients with intestinal failure.[30-32] in studies where results are reported in subgroups of patients with intestinal failure, average proportions were calculated first.

METHODS

A PubMed literature search for articles published after 2000 was performed using the following terms: IF, microbiome, microbiota, SCFAs, SBS, and PN. Literature search was restricted to human studies only. References from the selected manuscripts were searched for additional relevant publications. In addition, the literature was evaluated for associations with disease characteristics.

RESULTS

Factors influencing the microbiome in IF

Several factors can influence the gut microbiome in patients with IF (**Figure 2**). Gastrointestinal anatomy and physiology play an important role. Extensive small-bowel resection alters intestinal environment, including luminal pH and oxygen concentration, and enterohepatic circulation of bile acids.[33,34] A study in mice showed that small bowel resection caused Lactobacillus overgrowth, even when not receiving PN.[35] Korpela et al.[36] found that the length of the remaining small bowel was negatively associated with the abundance of *Lactobacillus plantarum* spp. Removal of the ileocecal valve predisposes the small intestine to overgrowth of bacteria, and removal of the ileum may lead to bile acid malabsorption. Bile acids have antimicrobial activity and may lead to a relative abundance of Firmicutes at the expense of Bacteroidetes.[37] The underlying primary disease itself may also be associated with an altered microbiome such as in Crohn's disease.[38-40]

During the phase of intestinal adaptation, oral/enteral nutrition (EN) is initiated as soon as possible to stimulate intestinal function. Factors that may have an effect on the gut microbiome include the type and consequently composition of oral or EN.[9,10] In addition, feeding tubes may act as loci for bacterial attachment and biofilm formation.[41,42] If no EN or oral nutrition is given, this has a substantial impact too. Ralls et al.[43] showed that EN deprivation in patients undergoing small-bowel resection (some receiving PN) led to overabundance of Proteobacteria.

In patients with IF, antibiotics are often used to treat small-intestinal bacterial overgrowth or central line-associated blood stream infections (CLABSI), which can influence the gut microbiome.[44-52] Next to antibiotics, other medications frequently used in IF such as proton pump inhibitors can also alter the gut microbiome.[53]

Microbiome in patients with IF

An overview of the results from studies investigating aspects of the gut microbiome in children and adults with IF or SBS is shown in **Table 1 and 2.** The primary aim of these studies was to characterize the gut microbiome composition in these patients. Almost all of these studies used 16S ribosomal RNA (rRNA) gene sequencing on fecal samples.

Alterations in gut microbiome composition

The most consistent finding among studies was an overall reduction in bacterial diversity.[30,32,36,54,55] However, Wang et al.[32] found that the global microbiome diversity, as evaluated by the Shannon index, in infants with SBS without complications [defined as IF associated liver disease (IFALD) or CLABSI] was similar to that of healthy controls.

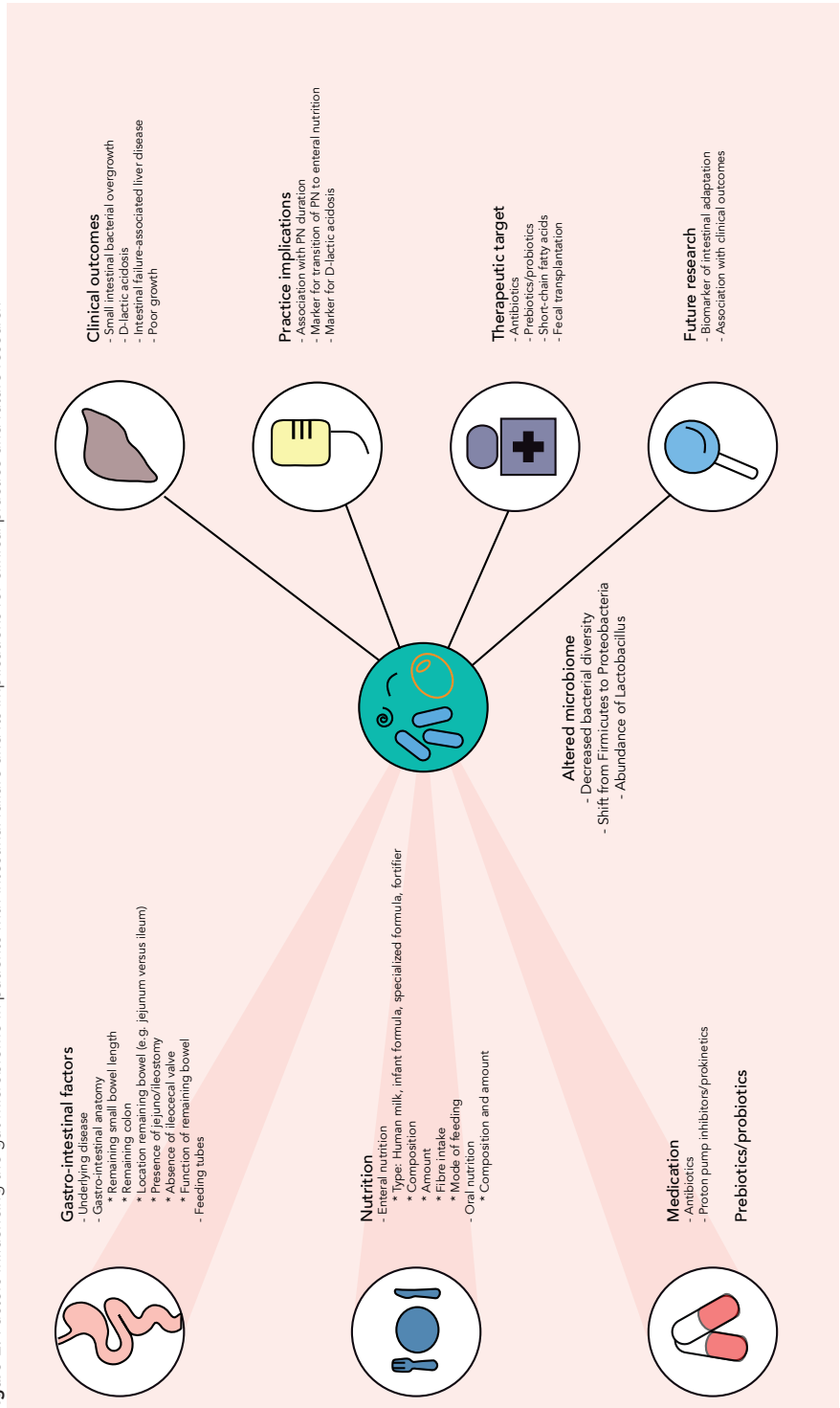


Figure 2. Factors influencing the gut microbiome in patients with intestinal failure and its implications for clinical practice and future research

Abbreviation: PN, parenteral nutrition.

Table 1. Studies about the gut microbiome in children with intestinal failure

Authors	Participants	Methods	Findings
Korpela et al. 2017	23 children with IF (median age 9.3 years (IQR 4.6-17)) - 17 weaned off PN 58 healthy controls - 3 months old infants (n = 11) - 2 to 6 year old children (n = 35) - Adults (n = 12)	Fecal samples Culture-independent phylogenetic DNA-based microarray analysis	• ↓ diversity and richness • ↑ Lactobacilli, Proteobacteria and Actinobacteria, Clostridium clusters IX, XIII and XV, Fusobacteria, Spirochaetes • ↓ Clostridium clusters III, IV and XIVa • Liver steatosis : ↓ diversity and richness • Patients with steatosis from grade 0 to grade 1: ↑ Proteobacteria, Fusobacteria and low levels of Clostridium • Patients with moderate to severe steatosis (grade 2-3): ↑ Bacilli and Actinobacteria
Wang et al. 2017	18 children with SBS (2-9 months) - All dependent on PN - 14 samples in IFALD group - 5 samples in CLABSI group - 7 samples asymptomatic group 7 healthy controls (4-10 months)	Fecal samples 16S rRNA sequencing Measurement of SCFAs	• ↓ richness in all SBS groups • ↓ diversity in IFALD and CLABSI group compared to asymptomatic SBS patients and healthy controls • IFALD/CLABSI group: ↑ Proteobacteria, ↓ Actinobacteria compared to asymptomatic group • Lower levels of acetate in SBS groups, equal propionate and butyrate and total SCFAs
Piper et al. 2017	8 children with SBS (0.7 – 11.3 years) - 3 weaned off PN - 3 with good growth - 5 with poor growth 3 healthy controls (0.5 – 2.3 years)	Fecal samples 16S rRNA sequencing Metagenomics shotgun sequencing	• ↓ Firmicutes order Clostridiales • Children with SBS and poor growth depletion of Firmicutes, expansion of Enterobacteriaceae • SBS/poor growth: deficient in genes needed for gluconeogenesis, enriched in branched and aromatic amino acid synthesis and citrate cycle pathway genes
Davidovics et al. 2016	9 children with SBS (4 months to 4 years) 8 healthy controls (7-8 years)	Fecal samples 16S rRNA sequencing	• Most dominant phyla Firmicutes, followed by Bacteroidetes, ↑ relative abundance of Proteobacteria and Gammaproteobacteria and Bacilli • Healthy controls ↑ Actinobacteria • Children with SBS and diarrhea ↑ Lactobacillus compared to children without diarrhea
Engstrand Lilja et al. 2015	11 children with IF (1.5 – 7 years) - 6 weaned off PN 7 healthy controls (siblings, 2-13 years)	Fecal samples 16S rRNA sequencing	• ↓ bacterial diversity in children with SBS on PN versus children weaned off PN • Patients with suspected SIBO ↑ Enterobacteriaceae, patient on PN without suspected SIBO ↑ Lactobacillaceae

Legend: Literature published after 2000, case reports excluded.
Abbreviations: CLABSI, central line-associated bloodstream infection; IF, intestinal failure; IFALD, intestinal failure-associated liver disease; PN, parenteral nutrition; SBS, short bowel syndrome; SCFAs, short-chain fatty acids; SIBO, small intestinal bacterial overgrowth.

Table 2. Studies about the gut microbiome in adults with intestinal failure

Authors	Participants	Methods	Findings
Gillard et al. 2017	17 adults with SBS - 9 lactate accumulating, - 7 non-lactate accumulating - 1 with recurrent D-lactic encephalopathy 6 rats with SBS 4 control rats	Fecal samples Real-time quantitative PCR Pyrosequencing Measurement of SCFAs	• Most abundant phyla: Firmicutes, followed by Proteobacteria, Bacteroidetes and Actinobacteria • Lactate accumulating patients: ↓ total SCFAs, ↓ propionate, equal acetate and butyrate • Lactate-accumulating group: ↑ lactate producing bacteria, ↓ lactate-consuming bacteria
Huang et al. 2017	5 adults with type II SBS 5 adults with type III SBS - 2 patients weaned off PN 5 healthy controls	Fecal samples 16S rRNA sequencing	• ↓ diversity • Type II SBS: ↓ Firmicutes and Bacteroidetes, ↑ Proteobacteria compared to healthy controls • Type III SBS: ↑ Bacteroidetes compared to healthy controls • Both type II and III: ↓ Lachnospiraceae, Ruminococcaceae, Peptostreptococcaceae, ↑ Enterococcaceae
Boccia et al. 2017	12 adults with SBS 16 healthy controls	Fecal samples Culture-dependent method Quantitative real-time PCR	• ↓ bacterial counts • ↓ Bacteroidetes, Firmicutes, Bifidobacterium and Methanobrevibacter Smithii
Mayeur et al. 2013	16 adults with type II SBS - 9 lactate accumulating in feces - 7 non-lactate accumulating in feces	Fecal samples Culture analyses and dominant bacterial groups were quantified by real time PCR Measurement of D and L-lactate levels in vitro cultures of bacterial strains and directly in fecal samples	• Predominant bacteria: Lactobacillus/Leuconostoc, ↓ Clostridium and Bacteroidetes • No difference in Lactobacillus between lactate-accumulating and non-lactate accumulating group • Non-accumulator group ↑ Lactobacillus Mucosae
Joly et al. 2010	11 adults with type II SBS 8 healthy controls	Fecal samples and mucosal biopsies Temporal temperature gradient gel electrophoresis Quantitative PCR	• ↓ diversity • High prevalence of Lactobacillus • Poor diversity of Clostridium leptum, Clostridium coccoides and Bacteroidetes • Lactobacillus mucosae detected in patients, not in healthy controls

Legend: Literature published after 2000, case reports excluded. Based on the anatomy of the remaining intestine, SBS is frequently divided into three categories: end-jejunostomy (type 1), jejuno-colic anastomosis where the remnant jejunum is in continuity with part of the colon (type II), and jejuno-ileal anastomosis with ileocecal valve and intact colon in continuity (type III).[2]
Abbreviations: PN, parenteral nutrition; SBS, short bowel syndrome; SCFAs, short-chain fatty acids.

Table 3. Cumulative summary of findings of studies on gut microbiome in patients with intestinal failure

Finding	Studies
↓ **Diversity**	Joly et al. 2010 [54¶] Engstrand Lilja et al. 2015 [55] Huang et al. 2017 [30] Korpela et al. 2017 [36¶] Wang et al. 2017 (in IFALD and CLABSI group) [32]
↓ **Richness**	Huang et al. 2017 [30] Korpela et al. 2017 [36¶] Wang et al. 2017 [32]
↓ **Total bacterial count**	Boccia et al. 2016 [56]
↓ **Number of species**	Wang et al. 2017 (in IFALD and CLABSI group) [32]
↑ **Proteobacteria**	Davidovics et al. 2016 [31] Huang et al. 2017 (in SBS type II patients) [30] Korpela et al. 2017 [36] Wang et al. 2017 (in IFALD and CLABSI group) [32]
↑ Gammaproteobacteria	Davidovics et al. 2016 [31]
↑ Enterobacteriaceae	Engstrand Lilja et al. 2015 [55¶] Piper et al. 2016 [20] Huang et al. 2017 (in SBS type II patients) [30] Wang et al. 2017 (IFALD and CLABSI group) [32¶, †]
↓ **Firmicutes**	Boccia et al. 2016 [56] Piper et al. 2016 [20¶] Huang et al. 2017 (in SBS type II patients) [30]
↑ Bacilli/Lactobacillaceae/Lactobacillus	Joly et al. 2010 [54¶] Mayeur et al. 2013 [57¶,†] Davidovics et al. 2016 [31] Gillard et al. 2017 [58¶,†] Huang et al. 2017 [30] Korpela et al. 2017 [36] Wang et al. 2017 (in IFALD and CLABSI patients) [32†]
Detection of *Lactobacillus mucosae*	Joly et al. 2010 [54¶] Mayeur et al. 2013 [57¶,†]
↑ Enterococcaceae	Huang et al. 2017 [30]
↑ Veillonellaceae	Wang et al. 2017 (in asymptomatic and IFALD patients) [32†]
↑ Clostridium clusters IX, XIII and XV	Korpela et al. 2017 [36]
↓ Clostridium clusters III, IV, XIVa bacteria	Korpela et al. 2017 [36]
↓ Clostridiales	Piper et al. 2016 [20]
↓ *Clostridium leptum, Clostridium coccoides*	Joly et al. 2010 [54¶]
↓ Lachnospiraceae	Huang et al. 2017 [30]
↓ Ruminococcaceae	Huang et al. 2017 [30]
↓ Peptostreptococcacae	Huang et al. 2017 [30]
↓ Erysipelotrichaceae	Huang et al. 2017 [30]
↓ **Bacteroidetes**	Joly et al. 2010 [54] Boccia et al. 2016 [56] Huang et al. 2017 (in SBS type II patients) [30] Wang et al. 2017 [32†]
↑ **Bacteroidetes**	Huang et al. 2017 (in SBS type III patients) [30]
↓ **Actinobacteria**	Davidovics et al. 2016 [31]

Table 3. Cumulative summary of findings of studies on gut microbiome in patients with intestinal failure (continued)

Finding	Studies
↑ **Actinobacteria**	Korpela et al. 2017 [36]
↓ Bifidobacterium	Boccia et al. 2016 [56]
↓ *Methanobrevibacter Smithii*	Boccia et al. 2016 [56]
↑ **Fusobacteria**	Korpela et al. 2017 [36]

Legend: Richness: Number of different species represented in gut microbiome; Diversity: A metric of species richness and their species evenness (i.e. how close in numbers each species is in a community). Based on the anatomy of the remaining intestine, SBS is frequently divided into three categories: end-jejunostomy (type 1), jejuno-colic anastomosis where the remnant jejunum is in continuity with part of the colon (type II), and jejuno-ileal anastomosis with ileocecal valve and intact colon in continuity (type III).[2] Only differences are reported. ¶ No p-values mentioned. † No comparison with healthy controls.
Abbreviations: CLABSI, central line-associated bloodstream infection; IFALD, intestinal failure-associated liver disease; SBS, short bowel syndrome..

Apart from a reduction in bacterial diversity, several studies also reported a reduction in bacterial richness, with the number of species representing the gut microbial community.[32,36] The results of studies in children are in accordance with those in adults.

Looking at compositional changes, most studies found a striking increase of gram-negative Proteobacteria, especially Gammaproteobacteria and their family Enterobacteriaceae (**Figure 1, Table 3**).[20,30-32,36,55] In healthy people, Proteobacteria represent a very small proportion of the intestinal microbiome (1-2%), but in patients with IF these species become a dominant member of the community. The overabundance of Proteobacteria during treatment with PN may be caused by lack of dietary fermentable substrate, such as fiber and resistance starch, in the gut lumen, necessary for growth of certain dominant species. This "gut starvation" effect and lack of interspecies competition offers the opportunity for subdominant species in the microbial community to increase over its dominant members.

In addition, a depletion of Bacteroidetes was found[30,32,54,56], and patients with IF presented low levels of Firmicutes of the order Clostridiales.[20,36,54] Another prominent difference from healthy controls is the overabundance of Bacilli, mainly Lactobacillus.[30-32,36,54,55,57,58] The increase in Lactobacillus is an important difference because in healthy subjects this group contributes <1% to the gut microbiome. The clinical significance of the increase in Lactobacillus remains unknown. One study reported that dominance of *Lactobacillus plantarum* spp. was associated with a relatively long PN duration before the possibility to wean off PN (i.e. successful intestinal adaptation)[36], whereas another study reported that this was associated with shorter PN duration.[30] In addition, depletion of Lactobacillus was associated with poor growth.[20] Other studies found that high levels of Lactobacillus were associated with diarrhea[31] and certain strains may cause D-lactic acidosis.[57] Certain strains like *Lactobacillus mucosae* were found in adults with SBS while this species has hardly ever been described in healthy humans.[54,57]

Alterations in microbiome functionality

Little is known about the metabolic activity of the gut microbiome of patients with IF. A previous study in children with IF showed that the fecal concentration of acetate was lower in children with IF compared to healthy controls, whereas there was no difference in propionate, butyrate, and total SCFA levels.[32]

In adults with a jejunocolic anastomosis, the abundance of *Clostridium leptum* and *Clostridium coccoides*, main butyrate-producing bacteria[59], was low.[54,57] Other studies also found low levels of butyrate-producing bacteria in patients with IF[36,58] or low levels of Firmicutes, known as major fiber fermenters.[20,30,56] Deficiency or depletion of these bacteria may affect the concentration of butyrate, an SCFA with established anti-inflammatory properties, and a major energy substrate for the intestinal epithelium of the colon.[60,61] However, in the aforementioned study, butyrate levels were not different in children with IF compared with healthy children.[32] A possible explanation for this might be that there is increased cross-feeding between acetate-producing and acetate-utilizing bacteria[62], hence acetate is used to produce butyrate[61], although more evidence is needed to confirm these findings.

The only study that used shotgun metagenomics sequencing found differences in carbohydrate metabolizing genes between patients with SBS and healthy control subjects. The gut microbiome of children with SBS was deficient in genes needed for gluconeogenesis but enriched in branched and aromatic amino acid synthesis and citrate cycle pathways.[20]

In addition to limitations pertinent to the laboratory methodologies used, there are also limitations due to the lack of clinical metadata potentially affecting microbiome characteristics and a scarcity of published data exploring clinically important associations. For example, information about the amount and type of EN/oral nutrition was often not reported. Because IF is a rare disease, most of the studies had small sample sizes and heterogeneous population characteristics. Most studies were of cross-sectional design, and prospective studies assessing the microbial changes in patients with IF during the process of intestinal adaptation are lacking. Therefore, there is a need for large, international, multicenter studies where successive data and samples will be collected prospectively from diagnosis and throughout the course of the disease.

Difference between patients on PN versus patients who have successfully weaned off

Patients with successful intestinal adaptation are able to stop PN; therefore, it is of interest to know if their gut microbiome is different compared to patients unable to wean off of PN and healthy control subjects. This is particularly important to explore because it may offer an opportunity to use gut microbiome characteristics as prognostic

biomarkers of intestinal adaptation or potentially manipulate gut microbial colonization with therapeutic interventions.

Although it was not the primary objective of the current literature, some authors described differences of the gut microbiome between patients with IF receiving PN and patients weaned off of PN. Engstrand Lilja et al.[55] found that microbiome diversity was significantly reduced in children with SBS receiving PN compared to children weaned off of PN. However, the diversity in children weaned off was still lower than that of healthy control subjects. They also found that children receiving PN had a higher relative abundance of Enterobacteriaceae than children weaned off of PN and control subjects. This is in line with the study of Korpela et al.[36], showing that most patients with a high abundance of Proteobacteria were still receiving PN and had received PN for a prolonged duration, whereas most patients with a high abundance of Clostridium cluster XIVa had weaned off of PN several years earlier and had been receiving PN for a limited time. Also Huang et al.[30] showed that Enterobacteriaceae was correlated with a longer PN duration, whereas predominance of Lactobacillus was associated with a shorter PN duration. In contrast, Piper et al.[20] found that there was no significant difference in potentially proinflammatory bacteria belonging to Enterobacteriaceae between children receiving PN versus children weaned off of PN.

These early data suggest that patients with IF able to wean off of PN have a gut microbiome more similar to healthy control subjects than patients who are unable to stop PN. However, analysis comparing patient characteristics between children weaned off of PN vs children not able to wean off were not performed, probably due to the small sample sizes and high heterogeneity. Differences in the gut microbiome could also be due to reverse causality and availability of luminal nutrients for bacterial growth from initiation of EN/oral nutrition. In the current literature, the duration of time that the patients had been weaned off of PN was often not known, and it is unknown if their diet was comparable to healthy control subjects.

Gut microbiome in IF and clinical outcomes

D-lactic acidosis

Small-intestinal bacterial overgrowth is a common complication in patients with IF that has direct impact on morbidity and mortality[63,64], and has been associated with dependence on PN.[65] Overgrowth of gram-positive anaerobes in the colon such as Lactobacilli, as well as poor metabolism of D-lactic acid and transfer in circulation can cause D-lactic acidosis. This is an unusual form of lactic acidosis in patients with SBS that may lead to neurological symptoms.[66-68] Treatment includes antibiotics, correction of metabolic acidosis, and restricting oral/enteral intake of carbohydrates.[69,70] Recently, a case report

has been published in which a 15-year-old patient with SBS suffering from recurrent D-lactic acidosis was successfully treated with fecal transplantation.[71]

Intestinal failure-associated liver disease

Many factors have been implicated in the development of intestinal failure-associated liver disease (IFALD).[72-74] Recent studies suggest that decrease in microbial diversity and overgrowth of certain bacterial groups are associated with IFALD. Korpela et al.[36] showed that increased abundance of Proteobacteria was strongly associated with liver steatosis, portal and intestinal inflammation, and liver fibrosis. The effect of the gut microbiome on liver steatosis in patients with IF was more predictive than the duration of PN or length of the residual intestine. Wang et al.[32] also showed that overrepresentation of Proteobacteria was common in children with IFALD. Many species belonging to Proteobacteria are opportunistic pathogens, such as *Escherichia coli*. A possible mechanism by which Proteobacteria may induce liver injury is via gut-derived lipopolysaccharide (LPS). LPS is a potent hepatotoxic inflammatory compound originating from gram-negative bacteria in the gut microbiota, including Proteobacteria. It normally penetrates the intestinal mucosa in trace amounts, enters the portal circulation, and becomes cleared in the liver. LPS has been involved in the pathogenesis of non-alcoholic fatty liver disease, leading to activation of toll-like receptors, promoting inflammation and fibrogenesis.[75,76] It is therefore possible that the increased abundance on Proteobacteria in patients with IF in conjunction with a compromised intestinal barrier function expose liver to higher, than normal concentrations of LPS.[77-79] Another group of bacteria that may cause liver damage are species belonging to Lactobacillus that may promote liver steatosis via excessive bile acid deconjugation.[36]

Poor growth

Piper et al.[20] showed that, from a small number of participants, children with SBS and poor growth (defined as decline in their weight z-score) had a depletion of the bacterial phylum Firmicutes compared with patients with SBS and good growth. However, the causal direction of this association is difficult to establish. It is possible that Firmicutes can harvest energy from fermentation of indigestible or malabsorbed nutrients and make it indirectly available to the host.[80] It is, however, equally possible that gut starvation from PN can deplete species that are dependent on the host's diet, such as Firmicutes, although the energy intake did not differ between children with poor vs good growth.

DISCUSSION

The microbiome as a biomarker of disease management in patients with IF

To date, there are no guidelines on the optimal timing for transition from PN to EN and there is not an ideal marker to use at present.[3] In the case of IF patients on PN treatment, changes in the gut microbiome during gut adaptation may potentially be used as biomarkers to judge the optimal time of transition from PN to EN. Prospective studies are required to assess longitudinal changes of the microbiome and their metabolic products in patients with IF undergoing gradual gut adaptation. The biomarker of choice to use in routine clinical practice should be quick to measure and the costs should be low. Current, yet limited, evidence suggests that SCFAs are altered in patients with IF. Considering their dependency on host diet and speed and the low cost of measuring them, they may fulfil the criteria of a biomarker to dictate the timing of introduction and advancement of EN. This hypothesis needs to be confirmed formally in well-designed prospective studies.

Next to the use of the gut microbiome as a biomarker for intestinal adaptation and advancement of EN, the microbiome might also be used to screen for risk for D-lactic acidosis. Mayeur et al.[57] suggest that the D/L fecal lactate ratio seems to be a proxy index for changes in the microbiome of patients with SBS and might be used to detect patients at risk for D-lactic acidosis. In a more recent study, they reported that patients accumulating lactate in their feces had more lactate-producing bacteria and a lower proportion of lactate-consuming bacteria, suggesting that the microbiome could be used to detect patients at risk of accumulation of lactate.[58]

Microbial therapeutic interventions in IF

The dysbiotic IF microbiome may be a therapeutic target for modulation. Potent interventions to manipulate the gut microbiome include the use of pharmacological doses of SCFAs, prebiotics, probiotics, antibiotics, and fecal transplantation.

Because SCFAs promote cell proliferation and differentiation of colonocytes, prevent growth of opportunistic pathogens and are key regulators of immune response [22,28] it might be beneficial to use SCFAs as a trophic factor to stimulate and promote intestinal adaptation. Previous studies in animals showed that supplementation of PN solutions with butyrate or mixed SCFAs may enhance intestinal adaptation[81-84], an effect which is mediated by upregulation of glucagon like petide-2 (GLP-2)[85], an intestinal trophic peptide. However, the role of SCFAs in this process is not always well established. In necrotizing enterocolitis, increased concentration of butyrate was associated with impaired barrier function, whereas in low levels it seemed to be of benefit to the host.[86]

Beyond the use of SCFAs, a study in piglets showed that intestinal adaptation was stimulated by prebiotic or synbiotic supplementation.[87] Limited evidence suggests that synbiotics may increase fecal SCFA levels and fecal levels of Bifidobacteria, total facultative anaerobic bacteria, Enterobacteriaceae, and Lactobacilli.[88] In a case report of a patient with SBS and recurrent episodes of neurologic dysfunction due to D-lactic acidosis, treatment with synbiotics was associated with a decline in D-lactate and the patient was free of recurrent episodes for 3 years without dietary restriction.[89] However, cases of bacteremia with prescribed probiotic bacteria in infants with SBS have also been reported.[90] Treatment with *Lactobacillus rhamnosus* had no effects on intestinal permeability, and was associated with a positive breath hydrogen test in a single patient.[91] Because the efficacy of probiotics in patients with SBS has not yet been adequately assessed, routine use of probiotics is currently not recommended in clinical practice.[92] The effect of fiber or prebiotic supplementation has not been explored in patients with IF on PN and might not be indicated in patients at risk of bacterial overgrowth.

Fecal transplantation has been first developed for the treatment of patients with chronic *Clostridium difficile* infection after failure to respond to antibiotic therapy.[93] Recently, a child with SBS and recurrent, therapy-resistant, D-lactic acidosis was successfully treated with fecal transplantation.[71] Fecal transplantation could therefore be a treatment alternative in selected patients with IF/SBS with dysbiosis who are at risk of D-lactic acidosis. However, risks associated with fecal transplantation such as bacterial translocation and septic shock are currently unknown, as well as the duration of the effect.

CONCLUSION

Patients with IF have an altered gut microbiome and altered metabolic activity. Although the amount of literature is small, the current evidence is remarkably consistent. Despite differences in the primary pathology and underlying disease the effect of IF on gut microbiome is very similar with profound shifts with an increase of Proteobacteria, especially Enterobacteriaceae, and a decrease of Bacteroidetes and often Firmicutes. Bacterial diversity is remarkably decreased, and there is high abundance of Lactobacillus. The changes found in children are in accordance with those in adults. Differences in microbiome characteristics have been found between patients receiving PN and those whose guts have adapted and have been weaned off of PN. There is potential to use the gut microbiome as a biomarker to guide clinical practice during intestinal adaptation as well as a modifiable therapeutic target.

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