THE PATHOLOGICAL MICROBIOTA

Intestinal microbiota in short bowel syndrome ✯

Microbiote intestinal dans le syndrome du grêle court

O. Goulet a,c,*, F. Joly b,c

a Department of Pediatric Gastroenterology, Hepatology and Nutrition, Hospital Necker - Enfants Malades, University of Paris- Descartes, Paris, France
b Department of Gastroenterology and Nutrition, Hospital Beaujon, University of Paris - Pierre et Marie Curie, Paris, France
c National Reference Center for Rare Digestive Disease

Summary  Short bowel syndrome (SBS) is the main cause of intestinal failure especially in children. The colon is a crucial partner for small intestine adaptation and function in patients who have undergone extensive small bowel resection. However, SBS predisposes the patient to small intestine bacterial overgrowth (SIBO), explaining its high prevalence in patients with this disorder. SIBO may significantly compromise digestive and absorptive functions and may delay or prevent weaning from total parenteral nutrition (TPN). Moreover, SIBO may be one of the causes of intestinal failure-associated liver disease, requiring liver transplantation in some cases. Traditional tests for assessing SIBO may be unreliable in SBS patients. Management of SIBO with antibiotic therapy as a first-line approach remains a matter of debate, while other approaches, including probiotics, offer potential based on experimental evidence, though only few data from human studies are available.

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Résumé  Le syndrome du grêle court (SGC) est la principale cause d’insuffisance intestinale, particulièrement chez l’enfant. Le côlon joue un rôle crucial pour l’adaptation et le fonctionnement de l’intestin grêle chez les patients qui ont eu une résection étendue de l’intestin grêle. Cependant, le SGC prédispose à une pullulation bactérienne dans l’intestin grêle (PBIG), expliquant son importante prévalence chez ces patients. La PBIG peut altérer significativement les fonctions de digestion et d’absorption intestinales peut retarder ou empêcher l’arrêt de la nutrition parentérale totale. De plus, la PBIG peut être l’une des causes de complications hépatiques associées à l’insuffisance intestinale, pouvant nécessiter le recours à une transplantation hépatique dans certains cas. Les tests cliniques habituellement utilisés pour évaluer la PBIG sont généralement peu fiables chez les patients avec SGC. Le traitement de la PBIG par une antibiothérapie de première intention reste très débattu, alors que d’autres approches, incluant les probiotiques,

*Corresponding author.
E-mail address: olivier.goulet@nck.aphp.fr (O. Goulet)
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Introduction

Intestinal microbiota (IM) has an influence on a variety of intestinal functions, including the development and maturation of the mucosal barrier and the mucosal immune system (see paper by Cerf-Bensussan et al.). Short bowel syndrome (SBS) is the most well recognized cause of intestinal failure (IF) [1]. Patients who undergo extensive small bowel resection and are left with SBS are in a state of severe intestinal malabsorption requiring parenteral nutrition. Small intestine adaptation leading to intestinal autonomy is a physiological process in which the colon is a crucial partner. The colon, by hosting the greatest quantity of the microbiota, may adapt after small bowel resection. However, small intestine bacterial overgrowth (SIBO) with subsequent risks of translocation and gut-derived sepsis (GDS) may lead to intestinal failure-associated liver disease (IFALD). Strategies aiming to avoid or limit such liver injury are mandatory. However, due to their central role in adaptation after small bowel resection, IM should be preserved as much as possible especially for optimizing the function of the colon.

This short review aims to underline the central role of the colon and its microbiota in SBS and the risks related to pathologic changes in the colon leading to bacterial overgrowth.

Short bowel syndrome

Short bowel syndrome (SBS) is characterized by a state of malabsorption following extensive resection of the small bowel. The length of resection results in insufficient nutritional supply requiring artificial nutrition [2]. The functional consequences of SBS depend on the length, surface and site of the resected small intestine [3]. The cause of resection and age of the patient at the time of surgery also influence the capabilities of the remnant gut function and potential for adaptation [3-5]. In clinical trials and in clinical practice, SBS may be classified into 3 different types (Fig. 1): 1) type 1, with jejunostomy where the jejunum is left too short, i.e., < 40-50 cm; 2) type 2, corresponding to SBS left with jejunoileal anastomosis, which misses the terminal ileum and the ileocecal valve, and often at least the right colon; and 3) type 3, the most favorable with jejunoileal anastomosis that preserves the terminal ileum, the ileocecal valve and the entire colon. Within the framework of SBS, the colon, in relation to its microbial contents, becomes a central digestive and nutritional organ for preserving nutrients and producing trophic factors.

Nutritional support should aim to maintain an optimal nutritional status with normal growth and development, while for infants or children an emphasis is placed on acquiring or maintaining oral feeding skills. Parenteral nutrition (PN) is the cornerstone of management, but the intestine should provide as much nutrition as possible to the patient in order to improve the physiological processes of SB adaptation. Oral feeding using enhancement of GI secretions, salivary EGF release, or gallbladder motility is recommended. However the mode of feeding administration varies among different groups as to the optimal composition (elemental, semi-elemental or polymeric) and mode of delivery (gastric tube or oral feeding) [6, 7].

According to recent reports, more than 80% of infants and children now survive after extensive small bowel resection in the neonatal period [3-5]. Prognosis is related to anatomical factors including age-adjusted intestinal length, ileocecal valve and colon preservation and occurrence of cholestasis [3-5]. However, to date most data on morbidity and mortality in neonatal SBS are based on individual case series, including long patient recruitment time, selection bias, variable SBS definitions, failure to account for gestational age and incomplete follow-up. A cohort study reported that most of the deaths were caused by liver failure or sepsis and occurred within 1 year from the date of surgery [8]. A recent survey included 87 children who undergone extensive neonatal SB resection, followed-up over a mean 15-year period [5]. The overall survival was 89.7% and varied according to the date of birth. By multivariate analysis, PN duration is significantly influenced by the length of residual SB and the absence of ICV. After PN weaning, patients grow up normally, with normal puberty and final height as expected from genetic target height. Some patients that are permanently dependent on PN need other innovative rehabilitation therapies, bowel lengthening, growth factors, intestinal transplantation [9, 10].

Role of the colon in the short bowel syndrome

By the time the chyme has reached the colon, most of the nutrients and 80-90% of the water have been absorbed in the small intestine. At this point some electrolytes like sodium, magnesium and chloride are left as well as indigestible carbohydrates known as dietary fiber. The chyme is mixed with mucus and bacteria and becomes feces. The bacteria, by metabolizing dietary fibers, play a crucial role for nourishment of the colon and in sparing calories. Moreover, a healthy colon may absorb medium-chain triglycerides (MCTs) [11].

Short-chain fatty acids

Soluble non-starch polysaccharides and some starches pass undigested into the colon where colonic bacteria ferment them not only to hydrogen and methane (“gas”) but also to short-chain fatty acids (SCFAs). The main SCFAs are acetate, propionate and butyrate. They are absorbed by the colon.
and metabolized by the colonic epithelial cells as a source of energy [12-15]. It has been estimated that up to 3 MJ of energy can be absorbed each day by the adult human colon in the form of SCFAs [16, 17]. In animal models, supplementation of an elemental diet with pectin, which is fermented to SCFAs in the colon, improved adaptation of the small intestine and colon in SBS [18]. The supplementation of parenteral nutrition with SCFAs or their intracecal infusion reduced mucosal atrophy and intestinal immune dysfunction following massive small bowel resection [19-21].

In addition to their local effects, systemic SCFAs in animal studies can affect the motility of both the stomach and the ileum through neuroendocrine mechanisms, probably through the expression of proglucagon and peptide YY. Furthermore, both systemic and enteral SCFAs exert a trophic effect on the jejunum by increasing mucosal mass, DNA and villus height [12, 19, 22].

Role for energy salvage

Since SCFAs are the preferred energy source for colonocytes, in patients with SBS the colon becomes an important organ for energy salvage [23]. Approximately 75 mmol of SCFAs are produced from 10 g of unabsorbed carbohydrate. Patients with SBS, but intact colon in continuity were able to decrease fecal energy loss by 1.3-3.1 MJ/day (310-740 kcal) when they were fed a diet containing 60% carbohydrates [24]. Colonic metabolism of unabsorbed carbohydrates was indicated by decreased fecal carbohydrate losses in patients with colon in continuity. It is possible for an intact colon to absorb up to 2.2-4.9 MJ (525-1170 kcal) daily from dietary fiber [24-26]. Colonic energy absorption may also increase somewhat during the post-resection adaptation phase, related to increased colonic bacterial carbohydrate fermentation [27, 28]. This may be due to increased colonic bacteria in patients with SBS as well as an increase in the concentration or activity of various enzymes, such as galactosidase, over time during the adaptation period [28]. Because SCFAs stimulate sodium and water absorption, patients might be expected to experience decreased fecal fluid and sodium loss, but this is not always observed clinically [24, 29].

Restoration of intestinal continuity, such as re-anastomosis of the small intestine with the colon, should be done whenever possible. By improving water and electrolyte absorption, PN can then often be discontinued. In addition anastomosis enables colonic fermentation of unabsorbed carbohydrates from the small intestine to occur, being an important source of energy assimilation.

Morphological adaptation of the colon

In spite of small intestine malabsorption in patients with SBS, both hyperphagia and adaptation of the remaining colon improve patient outcomes. A recent study evaluated morphology, proliferation status and transporters’ expression level in the epithelium of the remaining colon of SBS adult patients compared to controls [30]. The targeted transporters were Na⁺/H⁺ exchangers (NHE2 and 3) and oligopeptide transporter (PepT1). Twelve adult patients with a jejunocolic anastomosis were studied at least two years after the last surgery and compared to 11 healthy controls. The depth of crypts and number of epithelial cells per crypt were quantified. The proliferating and apoptotic cell contents were evaluated by revealing Ki67, PCNA and caspase 3. NHE2, NHE3 and PepT1 mRNAs were quantified by quantitative RT-PCR. Hyperphagia, as well as severe malabsorption, was observed in SBS patients compared to controls. Crypt depth and the number of cells per crypt was 35 percent and 22 percent higher, respectively (p<0.005), whereas the proliferation and apoptotic levels per crypt were unchanged. PepT1 and NHE2 mRNA were unmodified; NHE3 mRNA was down-regulated near the anastomosis and unmodified distally. It seems that in hyperphagic SBS patients with severe malabsorption, adaptive colonic changes include

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**Figure 1** Anatomy of short bowel syndrome in neonates and children
an increased absorptive surface with an unchanged proliferative/apoptotic ratio and well-preserved absorption NHE2, NHE3 and PepT1 transporters mRNA levels [30].

The Intestinal microbiota in the short bowel syndrome

Changes in microbiota

The remnant colon and its associated microbiota play a major role in the outcome of patients with SBS. As mentioned before, preservation of the colon in SBS patients is essential for recovering energy and is consequently a determinant in reducing the need for PN. The essential role of the colon in SBS patients is linked to its own absorptive capability, its adaptive increased absorptive surface and the metabolic capability of the microbiota. Bacteriological analysis based on culture-dependent methods has found that the microbiota of SBS patients is mainly composed of Lactobacilli [31, 32], but neither qualitative nor quantitative information is available concerning the other main bacterial groups. By using TTGE analysis and quantitative PCR, a recent study in adult SBS patients showed that the dominant fecal and mucosal groups were mainly composed of Lactobacilli and, to a lesser extent, Bifidobacteria [33]. Bacteria that usually account for up to 90% of the normal microbial community were absent, e.g., Clostridium leptum or Clostridium cocoides, or were underrepresented, such as Bacteroidetes. Interestingly, Lactobacillus mucosa, a bacteria never detected in healthy humans, was present within the fecal and mucosa-associated microbiota of the SBS patients. L. mucosa is likely to be specific to SBS since it has never been described as part of the gut microbiota in healthy humans. New probiotics should ideally promote the presence of deficient phyla and restore a classical profile of microbiota. To fully explore the effect of these conceptually new probiotics, it is important to consider the overall composition of microbiota in SBS pathology. The changes in microbiota involving SBS patients should be extensively investigated and considered carefully since microbiota plays a central role in energy recovery by the colon. Experimental models of SBS have shown that butyrate is the SCFA that augments intestinal adaptation by increasing proliferation and decreasing apoptosis, while GLP-2 may be the mediator of the changes [34].

On the other hand, microbiota, which is as key factor in bowel function and adaptation, should always be carefully preserved by avoiding oral antibiotics as much as possible for bowel decontamination. SBS including ileocecal valve resection often leads to small intestinal bacterial overgrowth with the risk of liver disease. Management should promote surgical procedures such as bowel tapering and lengthening instead of aggressive enteral feeding and/or oral large spectrum antibiotic cocktails [8, 9].

Vitamin K synthesis

About 60% of vitamin K is synthesized by colonic bacteria [35]. Deficiency is therefore uncommon in patients with an intact colon. However, vitamin K deficiency may occur in patients left without colon, patients with protracted small intestine enterostomy or in those who received broad-spectrum antibiotics. The daily requirement in pediatric patients is 0.1mg/kg. Pediatric multivitamin parenteral formulations generally contain vitamin K.

D-lactic acidosis

D-lactic acidosis, also referred to as D-lactate encephalopathy, is a rare neurologic syndrome that occurs in individuals with SBS or following jejunoileal bypass surgery. Fortunately, this complication is very rare. Symptoms typically present after the ingestion of high-carbohydrate feedings. Neurologic symptoms include altered mental status, slurred speech and ataxia, with patients often appearing drunk. Onset of neurologic symptoms is accompanied by metabolic acidosis and elevation of D-lactate plasma concentration. L-lactate concentration, which is usually measured when serum lactate concentration is ordered, is normal. Thiamine deficiency should be excluded [36, 37].

Lactobacilli and other bacteria, including Clostridium perfringens and Streptococcus bovis, ferment unabsorbed carbohydrate to D-lactic acid, which cannot be metabolized by D-lactate dehydrogenase. These organisms may proliferate in an acidic environment that may be promoted by the metabolism of unabsorbed carbohydrates to SCFAs. The mechanism for the neurological symptoms is unknown. They have been attributed to D-lactate, but it is unclear if this is the cause or whether other factors are responsible [38]. Treatment described in case reports have included nothing (with spontaneous resolution), oral metronidazole, neomycin, vancomycin, (for 10-14 days) and avoidance of “refined” carbohydrates [39, 40]. However, one should consider the intestinal microbiota as a major factor for achieving intestinal adaptation and should be always “respected” and not be destroyed by unnecessary and/or inappropriate use of oral antibiotics.

Small intestinal bacterial overgrowth as a limiting factor in the short bowel syndrome

Consequences of small intestinal bacterial overgrowth (SIBO)

Functional factors such as absorption capability and intestinal motility of the remnant small intestine or small intestinal bacterial overgrowth (SIBO) emerge as essential components in the course of SBS patients. SIBO causes increased intestinal permeability, mucosal inflammation, allergic reactions and villous atrophy, which may further exacerbate nutrient malabsorption, deconjugate bile salts and deplete the bile salt pool with subsequent impaired micellar solubilization resulting in steatorrhea and fat soluble vitamin malabsorption [41-45]. SIBO increases the risk of intestinal bacterial translocation. It is usually associated with anorexia, vomiting, diarrhea, cramps, abdominal distension and failure to thrive.
Management of SIBO

Early detection and appropriate treatment of SIBO is necessary to avoid morbidity and mortality following these severe SBS complications [41]. SIBO exacerbates hepatotoxicity related to PN and is likely to occur in the case of ICV resection, poor motility of a dilated small bowel segment [9, 41, 42]. When possible, the performance of an intestinal tapering and lengthening procedure or resection of a tight anastomosis may be essential to obtaining SIBO resolution [8, 9].

Indeed, medical therapy is difficult since the use of prokinetic drugs for enhancing gut motor activity is contraindicated in these conditions. Antimotility agents such as loperamide may exacerbate SIBO and is also contraindicated. Antibiotics should be used very cautiously due to their effects on the colonic bacterial flora which should be preserved for production of SCFAs and trophic factors. Intermittent antimicrobial therapy based on oral metronidazole, either alone or in combination with trimethoprim-sulfamethoxazole, has been thought to be an effective approach. The use of broad-spectrum antimicrobial therapy must be very limited due to the high risk of emergent multiresistant strains of bacteria and the anti-physiologic effects on colonic bacterial flora [9].

Role of probiotics in SBS

The use of probiotics might be helpful in SBS pediatric patients [46]. However they should be used very cautiously because of the addition of exogenous flora to an already overgrown small bowel bacterial flora. Moreover, cases of Lactobacillus bacteremia during probiotic treatment of SBS pediatric patients have been reported [47-49]. Cases of S. boulardii fungemia have been reported in SBS patients with a central venous catheter (CVC) [50]; S. boulardii treatment is contra-indicated in patients with a CVC. However, the successful use of probiotics for the prevention of necrotizing enterocolitis in premature babies has been well documented [51, 52].

The effects of probiotics on bacterial translocation (BT) and mucosal intestinal trophicity after massive small bowel resection were studied in rat models. The effects of Saccharomyces boulardii versus placebo was studied in rats after 50% small bowel resections. S. boulardii significantly enhances the functional adaptation of the remaining intestinal segments as shown by jejunal mucosal protein content and brush-border enzymes [53]. In another experiment, probiotics decreased BT through mechanisms which may be dependent on intestinal mucosal integrity. In addition, SBS rats had a greater proliferation index and apoptotic index in both the jejunum and ileum compared with sham animals [54].

Intestinal permeability (IP) was assessed in SBS patients in a double-blind, placebo-controlled crossover clinical trial by using lactulose-to-mannitol ratio [55]. Twenty-one children (9 months to 17.5 years old) with SBS participated in the study. Nine children received a daily dose of 10 billion CFU of Lactobacillus rhamnosus (also known as LGG) or placebo for 4 weeks, followed by a 3-week washout before therapy was crossed-over for another 4 weeks. In this sample of children, the IP was within normal limits and did not correlate with age. LGG therapy had no consistent effects on IP.

Two open trials involving Saccharomyces boulardii (SB) administration were performed in SBS pediatric patients [56, 57]. Clinical symptoms including vomiting, abdominal pain and distension, bloating and flatulence, as well as abnormal hydrogen breath test, were assessed before and after the administration of high doses of SB (250 mg x 3 per day) for one month (Fig. 2). Both trials led to a significant decrease in the frequency and intensity of symptoms in patients with SBS. In the Neckler study, the disappearance of bacterial strains such as Klebsiella pneumoniae or Serratia marcescens as assessed by conventional stool cultures suggests that a one-month administration of SB may positively influence SIBO in patients with SBS.

Finally, understanding the colonic physiology and microbiota helps measure the importance played by both in the management of patients with SBS. The colon and its microbiota should be considered as partners rather than potential deleterious factors, even if SIBO related complications are limiting factors in the long-term survival of patients with SBS. Future developments in the field of probiotics might provide safe and targeted approaches in modulating microbiota.

Saccharomyces boulardii in SBS

Administration of 250 mg x 3/day in children

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Day 0 Day 28 Day 28Day 0

Figure 2. Improvement of clinical symptoms and breath test after administration of S. boulardii
SBS: short bowel syndrome

Conflicts of interests

O. Goulet: None
F. Joly: None

References


Intestinal microbiota in short bowel syndrome


