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Intestinal Failure and Short Bowel Syndrome in Crohn's Disease: A Systematic Review

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Abstract: Crohn's disease (CD) is an inflammatory, chronic and progressive disease that affects the digestive tract. Despite optimized drug therapy, the risk of multiple surgical interventions over the years is high, leading the patient to develop short bowel syndrome (SBS). Thus, adequate management in the postoperative period directly interferes with the long-term prognosis. Initially, most of these patients, due to hydro electrolytic disorders and absorptive incapacity inherent in SBS, will need parenteral nutritional support. According to the patient's residual digestive profile and according to nutritional management (oral, enteral, and/or parenteral), the intestine will evolve in its adaptive capacity. During this period, control agents are used for motility and intestinal secretion and, if necessary, GLP-2 agonists (intestinotrophic). In cases refractory to these treatments, we can still indicate surgical procedures to control motility, increasing intestinal length, and, finally, transplantation. CD is recurrent, and patients with SBS need a multidisciplinary approach with continuous monitoring to provide better intestinal rehabilitation and consequent quality of life.

Keywords: Intestinal failure, Short bowel syndrome, Crohn's disease, Nutritional support

Introduction

Crohn's disease (CD) is a chronic and progressive inflammatory disease, characterized by transmural involvement of the digestive tract. This is the reason for the frequent appearance of strictures, abscesses, and intestinal fistulas [1]. Despite advances in drug treatment, more than half of patients with CD will undergo intestinal resections in the next 10 years after diagnosis of the disease. Of these, one-third will still need a second intestinal resection in 5 years after the first procedure [2].

Since most patients develop the disease between adolescence and early adulthood, frequent resections may develop short bowel syndrome (SBS) and/or intestinal failure (IF). The risk factors for such situations are young age at diagnosis and first surgery, a disease with stenosis, family history of inflammatory bowel disease, smoking, and postoperative complications [3].

For these reasons, the CD is one of the most common causes of IF with the need for home parenteral nutrition (HPN). In the UK alone, it accounts for 25% of all causes of IF, while in Japan, a study revealed an incidence of IF of 3.6; 6.1, and 8.5% in 10, 15, and 20 years of illness, respectively. This situation is extremely morbid, with an important impact on quality of life [3].

In the last decade, the frequent use of biological agents in the treatment of CD has brought promising results, expecting a reduction in long-term surgical procedures with their use [4]. It still lacks data to support this hypothesis [5]. However, a population-based cohort study found a 2.2-fold lower risk for surgical intervention in the era of use of biological agents when compared to the era without the use of these drugs [4, 5].

Therefore, the present study aimed to discuss the epidemiological and pathological aspects of intestinal failure with short bowel syndrome in CD disease, with a focus on nutritional, drug, and surgical management.

Methods

Study Design

The rules of the Systematic Review-PRISMA Platform (Transparent reporting of systematic reviews

and meta-analysis-HTTP: //www.prisma-statement.org/) were followed [6].

Data sources and research strategy

The search strategies for this systematic review were based on the keywords (MeSH Terms): *"Intestinal failure. Short bowel syndrome. Crohn's disease. Nutritional support"*. The research was carried out in October 2018 to May 2019 and developed based on SCOPUS, PUBMED, and SCIENCE DIRECT, including the National Institutes of Health RePORTER Grant database and clinical trial records. Also, a combination of the keywords with the booleans "OR", AND and the operator "NOT" were used to target the scientific articles of interest. The title and abstracts were examined under all conditions.

Study Quality and Bias Risk

The quality of the studies was based on the GRADE instrument [7] and the risk of bias was analyzed according to the Cochrane instrument [8]. Two independent reviewers carried out research and study selection. Data extraction was performed by reviewer one and fully reviewed by reviewer two. A third investigator decided on some conflicting points and made the final decision to choose the articles. Only studies reported in English have been evaluated.

Results and Discussion

A total of 155 articles were found involving the *Intestinal Failure and Short Bowel Syndrome in Crohn's Disease*. Initially, duplication of articles was excluded. After this process, the abstracts were evaluated and a new exclusion was performed, removing articles that did not include the theme of this article. A total of 65 articles were evaluated in full and 20 were included in the systematic review (Figure 1).

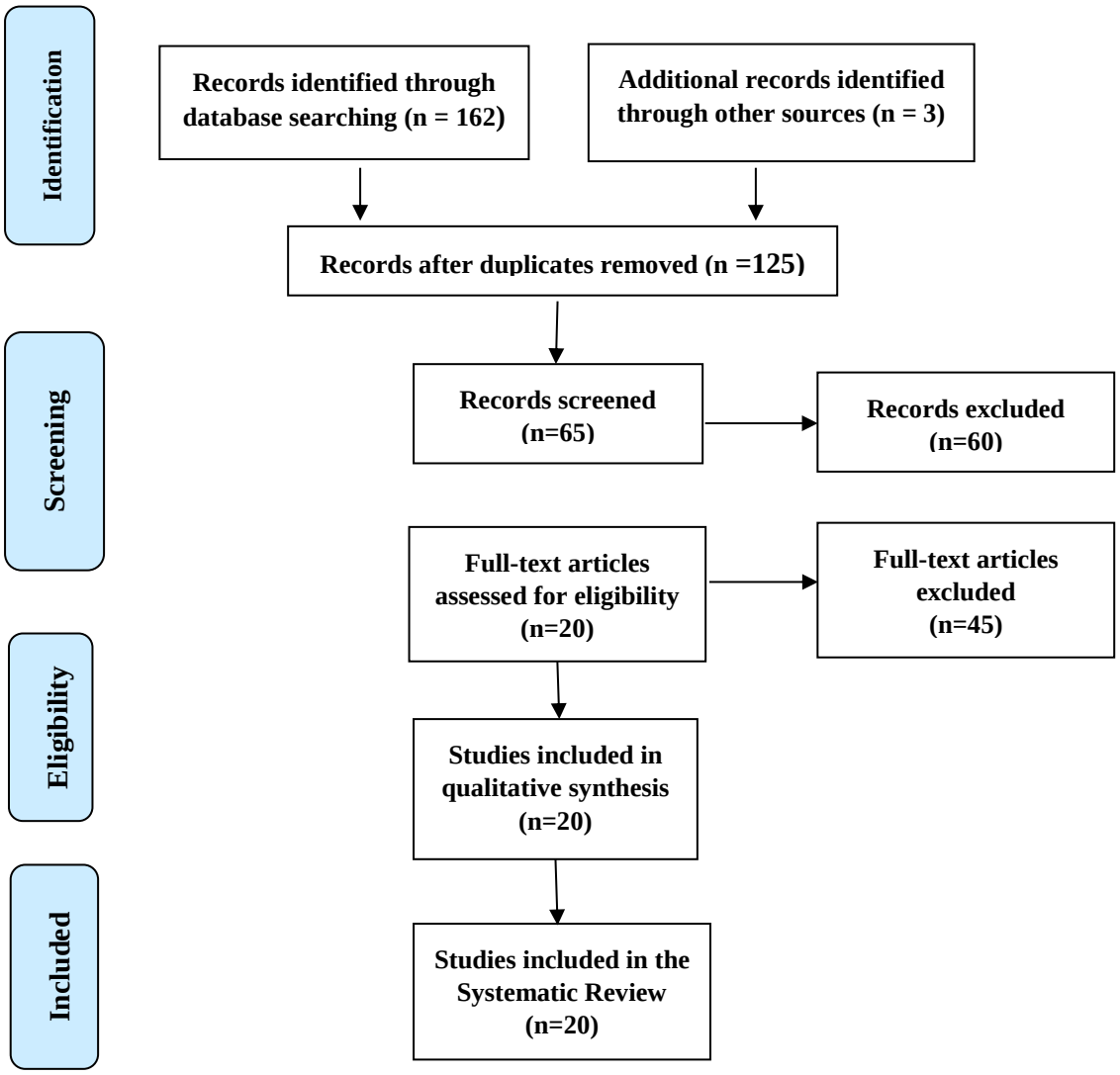

Figure 1. Study Eligibilit

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Considering the Cochrane tool for risk of bias, the overall assessment resulted in 1 study with a high risk of bias and 2 studies with uncertain risk. The domains that presented the highest risk of bias were related to the number of participants in each study addressed. Also, there was an absence of the source of funding in 2 studies and 3 studies did not disclose information about the conflict-of-interest statement.

After a thorough analysis of these selected studies, it was found that Crohn's disease has been increasing its occurrence worldwide in recent decades. This growth stands out mainly in developed countries and urban areas. Unlike other diseases, there is no differentiation between sexes in its occurrence [1].

The onset of CD occurs with higher rates between the second and fourth decade of life, with a small peak between 50 and 60 years [1]. It can reach frequencies as high as an incidence of 20.2 to 29.3 per 100,000 inhabitants/year, as is the case in Canada and Australia, and a prevalence of 322 (Europe) to 214 (United States) cases per 100,000 inhabitants [1]. Latin America also follows this growth, with the most expressive rates in Brazil, which revealed an increase in the incidence of CD from 0.08 (the year 1988) to 5.48/100,000 inhabitants/year in 2015 [9].

Although the proportion of surgical treatment in CD has been decreasing in recent years, the increase in its incidence continues to make it common to find patients with surgical complications. CD is among the main causes of intestinal failure requiring HPN. North American data from the 90's estimate that 11% of patients using HPN are caused by complications related to CD (second major cause) [5]. Although the prevalence of HPN has decreased in the United States (EU), in 2013 there was still an average of 79 cases million people and an increase of 2.5 times the use of household EN (1385/million inhabitants) when compared to the 1990s [10-13].

Among the 1115 adults who underwent bowel transplantation in the US between 1990 and 2014, short bowel syndrome was the most common indication (75%) for this procedure, which includes CD (13%), thrombosis, or vascular insufficiency (24%) [14].

Physiopathology

CD has multiple subtypes, which contribute to its observed clinical heterogeneity. This concept was reinforced by the recognition of the complexity of genetic, microbial, immune, and environmental factors that affect the risk of the disease, although the etiology is not fully understood, the CD is still classified as an inflammatory bowel disease with autoimmune pathophysiology.

Autoantibodies are activated against the function of the intestinal epithelial barrier and circulating antibodies are present in front of a variety of autoantigens, including lymphocyte antigens. The tumor necrosis factor (TNF) has a central role and the specific inhibition of this pleiotropic cytokine by biological anti-TNF agents has been a great advance in the treatment of CD [12].

An association has been demonstrated between CD and the NOD2 mutation ("nucleotide oligomeric domain 2"): the defect is responsible for an inadequate immune response, damaging function of the mucous barrier, and microbial dysbiosis. Thus, the hypothesis was raised that the deficiency of NOD2 leads to a microbial dysbiosis associated with the specific and transmissible mucosa, regardless of the defect of the mucosal barrier [12].

Since the risk of surgical intervention in CD increases progressively with the years of illness, the possibility of the appearance of SBS arises, followed by IF. The latter is characterized by temporary or permanent intestinal malabsorption. The most recent guidelines define IF as "a reduction in the intestinal function below the minimum required for the absorption of macronutrients and/or water and electrolytes so that intravenous supplementation is necessary to maintain health and/or growth" [13].

It is most often caused by short bowel syndrome (SBS), which occurs after the removal of half or more of the small intestine, therefore, SBS is the cause of 74% of patients in home parenteral nutrition and of this total, 29% are consequent to CD [15,16]. The risk for developing SBS after surgery on CD is closely related to the length of the remaining small intestine, preserving at least 200 cm of the small intestine can reduce the risk of SBS [3].

In this context, there are 3 recognized IF categories. The first is self-limited or "Type 1", which occurs more often after abdominal surgery and resolves with nutritional or liquid support in the short term. "Type 2" IF is associated with septic, metabolic

or nutritional complications of difficult surgical procedures in patients with CD or patients with mesenteric vascular disease [3]. Despite advances in intensive care, antibiotic therapy, and nutritional and metabolic support, IF Type 2 is still associated with considerable morbidity and mortality. Intensive care is crucial to reduce the likelihood of these patients developing "Type 3" IF, which is characterized by the need for long-term parenteral nutrition [3].

The most common reason for the development of type 3 IF in patients with CD is the inadvertent intestinal injury resulting from the management of type 2 IF that has developed as a complication of surgical resection. Preventing type 3 IF is, therefore, a fundamental objective for the surgeon who treats patients with type 2 IF. **Table 1** summarizes the types of intestinal failure, their description, examples, and management goals [17].

Table 1. Types of Intestinal Failure

Types	Description	Time	Examples	Management goals
Type I IF I Acute	Acute Condition. Others organic dysfunctions frequently present. Self-limited course when the others organic dysfunctions arecorrected	Days	Postoperative paralytic ileus or bankruptcy syndrome multiple organs.	Support acute illness. Stabilization of homeostasis. IF Resolution.
Type II IF II Acute	Acute condition prolonged. Continuity of instability metabolic	Weeks to months	Abdominal sepsis recurring with or without fistula. Phase acute short intestine.	Maintain clinical stability without sepsis or another organ dysfunction. IF resolution or evolution to IF chronic.
Type III IF Chronicle	Chronic organ failure without organic dysfunction acute. Condition of clinical stability.	Months to years	Gut syndrome I enjoy. Dysmotility intestinal	Maintenance of homeostasis. Nutritional and healing optimization of wounds. Restoration of intestinal integrity when possible.

*IF – Intestinal Failure. Adapted from reference No. 14.

Table 2. Predisposing Anatomy and Residual Length for Parenteral Nutrition Dependence*

Residual Intestinal Anatomy	Average length for dependence on parenteral nutrition
Terminal jejunostomy	< 100-115 cm
Jejunocolic anastomosis	< 60-65 cm
Jejunoileal anastomosis (colon in continuity)	< 30-35 cm

*Adapted from reference 2.

Therefore, the prognosis of SBS that will require HPN is directly related to the combination of the patient's digestive remnant. **Table 2** shows the thresholds for HPN dependence [2, 3, 17]. The presence of intestinal ileus is also a prognosis in the use of HPN. Resections greater than 100 cm of the ileum are related to insufficient absorption of bile salt, causing damage to the enterohepatic bile recirculation and the consequent impact on fat absorption. It also participates in enteric hormonal feedback mechanisms that delay gastric emptying, called "ileal brake" and regulate the migratory motor complex.

The absence of the "ileal brake" leads to faster intestinal transit and a reduction in the contact time for nutrient absorption. The presence of the ileocecal valve helps to reduce this flow, in addition to preventing the migration of bacteria from the colon, causing bacterial overgrowth. Also, hypersecretion of gastric acid and the "clearance" of gastric acid content in the duodenum impair the activity of pancreatic enzymes, subsequently contributing to the malabsorption of fat [2].

The colon's importance in preserving nutritional autonomy is related to its primary role in the absorption of fluids, electrolytes, and fatty acids. Normally, between 1 and 2 L of feces can enter the cecum every day, and the colon dramatically reduces up to 90% of the water content to 100 to 200 mL of feces. Colon bacteria also ferment indigestible carbohydrates into short-chain fatty acids, which serve

as a source of calories. Thus, the absence of the colon severely impairs fluid absorption and reduces short-chain fatty acids as a source of calories [2].

Intestinal Adaptation

Intestinal adaptation refers to a process by which this organ undergoes several structural and functional changes to compensate for the loss of intestinal function due to injury or resection. As a result, both the colon and the small intestine undergo metaplasia and hyperplasia, adapting to changes in the intestinal anatomy received [18].

Among the segments of the digestive tract, the ileum is more skilled in the ability to perform metaplasia of the colonic cells and in the growth of the villi to compensate for the absence of the colon. This, in turn, has an intermediate potential to develop ileal cells, while the jejunum has a weak potential for adaptation. These differences partially explain the significance of the ileum and the colon in preserving nutritional autonomy [2, 18].

In general, the entire process of intestinal adaptation usually occurs in 1 to 2 years, starting immediately after intestinal resection. It is inversely related to the time of use of parenteral nutritional support and direction to the use of enteral/oral diet. For this reason, the early use of the enteral diet is beneficial, even with a trophic infusion rate (15 to 25 mL/h) [2, 18].

Complications

Morbidity in SBS results mainly from the sequelae of malabsorption of fluids and nutrients, which occur mainly in the acute postoperative phase of intestinal resection; surgical complications, and the adverse effects of HPN. Especially in the acute phase, fluid resuscitation is essential in all patients with IF, and necessary before any nutritional intervention [17]. The small intestine usually absorbs 80% of the fluids received, while the colon 18%. However, the colon has the possibility of increasing its absorption capacity. Since fluid loss (diarrhea) is inversely proportional to the size of the remaining small intestine, the presence of the colon plays an important role in the water management of these patients in the postoperative period [14].

Thus, patients with terminal jejunostomy or proximal ileostomy often develop dehydration and electrolyte deficiencies (especially magnesium, potassium, and sodium). Normal electrolyte values must be achieved in all patients with IF, mainly because electrolyte disturbances can aggravate gastrointestinal dysmotility [19]. The resection of the ileum results in proportionally greater malabsorption and diarrhea than the loss of the jejunum, due in part to the excess of bile salts and unabsorbed fats that reach the colon and also because the jejunum is less able to adapt [17].

Patients on exclusive HPN are particularly at risk for vitamin, mineral, and trace element deficiencies if micronutrients are not monitored and replenished accordingly. For example, iron is not included in the parenteral nutrition (PN) due to compatibility problems and generally requires oral or parenteral supplementation [2].

Patients with SBS can develop hepatobiliary dysfunction for several reasons, including adverse effects of PN, nutritional deficiencies, bacterial overgrowth, sepsis, or concomitant liver disease, especially in patients with inflammatory bowel disease [20]. Liver steatosis can run as short as 2 weeks from the onset of PN, however, its course is reversible and I rarely progressed to cirrhosis. On the contrary, intrahepatic cholestasis can occur at a later time (> 3 weeks from the onset of PN) and is characterized by presenting lymphocytic infiltrate leading to cirrhosis and liver failure [2].

Deficiency of amino acids such as taurine, choline, carnitine, and glutamine, as well as essential fatty acids (linoleic and linolenic acid), can also contribute to liver damage. In addition to these aspects, it is sought to maintain a PN with an infusion of dextrose <5 mg/ kg/min as well as a lipid dose <1 kg/day, and to avoid excess calories [2,17].

The presence of cholelithiasis is another complication seen in SBS. This can be explained by reduced oral intake and consequent reduction of gallbladder contractions, as well as alteration of bilirubin metabolism, mucin hypersecretion, and cholesterol supersaturation. Clinical conditions are more severe when there is resection or ileal disease.

Another important complication to be highlighted is a bone mineral disease. It can be present in 40 to 100% of patients with intestinal failure [2] and 50% of patients with CD [21]. In this population, the presence of a very low body mass index (BMI), use of glucocorticoids, males, previous exposure to gastrointestinal surgery, and smoking are risk factors for the development of osteopenia and

osteoporosis [21, 22]. Thus, it is recommended to regularly monitor the levels of calcium and vitamin D, as well as their replacement when necessary [22]. In patients using HPN, bone densitometry is also recommended every 2 years [2].

Patients with SBS and the presence of the colon are at elevated risk (1.25 times higher) of developing nephrolithiasis due to calcium oxalate calculations, especially if there is concomitant ileal resection. The mechanism involved in the binding of calcium to unabsorbed fatty acids, leaving excess oxalate anions available for resorption in the colon. This in turn also shows an increase in permeability to small molecules, such as oxalate, induced by unabsorbed bile acids, facilitating the entry of oxalate into the bloodstream. A reduction in the bacterial degradation of oxalate due to the decrease in *Oxalobacter formigenes* also leads to an increase in its absorption. The combination of high serum oxalate concentrations, dehydration, acidic urinary pH, predisposes the patient to the formation of renal oxalate stones [2, 23].

Strategies to reduce the risk of nephrolithiasis include ideal hydration, increased calcium intake (or supplementation of 1 to 4g/day of calcium carbonate) in the diet, adherence to a diet low in oxalate and fat [2]. 24-hour oxaluria monitoring can also be used, as the risk of nephrolithiasis becomes high when the values exceed 25 mg/day. When necessary (presence of metabolic acidosis), potassium citrate can be used to alkalinize urine [23].

Finally, survival in patients with intestinal failure has been estimated at 94% and 80% at 1 and 4 years, respectively, and the main cause of death in these patients is usually sepsis and liver failure [2].

Nutritional Management

Nutrotherapeutic management requires a combination of nutritional, medication, and surgical support. The goal is to provide adequate intake of fluids and nutrients, minimizing complications and impact on quality of life. During the initial stages of SBS (acute phase), when the patient is unable to consume adequate fluids or nutrients orally, PN may be necessary. Oral and/or enteral nutrition should be started as soon as possible to promote intestinal rehabilitation, especially when diarrhea losses are less than 2.0-2.5 L/day. As intestinal adaptation (adaptive phase) occurs over successive years (1 to 2 years), the balance between oral and parenteral nutrition may evolve [2, 18].

Parenteral Nutrition

Among patients with SBS, PN has a fundamental performance in the following: postoperative, adaptation, and maintenance periods. Thus, in the postoperative period (PO), its main function is to guarantee all necessary protein, caloric, water, and micronutrient inputs. The patient will hardly be able to start any type of oral/enteral diet in the first 7 to 10 days of PO [2].

As the patient progresses with a reduction in the diarrheal condition, the adaptation phase is characterized by the transition period between PN and progression to oral/enteral diet. In some situations, there will still be a dependence on PN, despite the presence of the oral/enteral diet. At this moment, the maintenance and stabilization phase (adaptive phase) is outlined. Table 2 describes the anatomical profile of the digestive remnant that presents a high probability of dependence on household PN [2].

Enteral Nutrition

Whenever possible, the onset of the EN should be stimulated with the consequent weaning of the PN. The presence of EN through the gastrointestinal tract reduces intestinal permeability and atrophy, promoting intestinal adaptation.

The standard formula to be started is of the polymeric type. Semi-elementary formulas should be considered when polymeric formulations are not well tolerated. Other characteristics in the formula must include an osmolarity of 300 mOsm/L with 100 mmol/L of sodium [2].

In the adaptation phase, continuous EN can be used in small amounts if the intestinal losses are less than 2.5 L/d. The use of continuous EN has been shown to increase intestinal absorption in the early stages of intestinal adaptation. As an alternative, nocturnal EN can serve as a complement to a suboptimal oral intake (OI). As in the adaptation phase, if the patient is unable to maintain an adequate OI, nocturnal supplementation of EN can be considered [2].

Oral Diet

The most important aspect for dietary management in patients with SBS is to encourage hyperphagia or an OI greater than 1.5-2 times what they were used to eating before the development of SBS. Relative malabsorption can be overcome to some extent with greater intake [16]. The general nutritional principles that apply to all patients with SBS include

the separation of food and liquids during meals, implementation of smaller and more frequent meals, and reduced intake of foods with high osmotic properties (for example, concentrated sweets). Other nutritional interventions can be individualized according to the type and length of the patient's residual intestinal anatomy (**Table 3**).

For patients with continuing colon, the consumption of complex carbohydrates can provide additional calories by bacterial fermentation in short-chain fatty acids. The restriction of fat and oxalate intake, associated with good hydration, is important to reduce the risk of nephrolithiasis (**Table 4**). On the other hand, for those with terminal ostomy of the small intestine,

Table 3. Nutrotherapeutic recommendations in patients with SBS in the presence and/or absence of colon

Type of Diet	Terminal Ostomy (without colon)	Colon intact
Carbohydrates	Limit concentrated sweets.	Limit concentrated sweets. Favor complex carbohydrates.
Fats	Without restriction, unless there is steatorrhea.	Limit.
Oxalate	Absence of restriction.	Restrict.
Fiber	Limit if diarrhea gets worse.	Absence of restriction. Favor soluble fibers over insoluble fibers.

*Adapted from reference 2.

Table 4. Oxalate-containing foods

Food Category	Oxalate-Rich Foods
Miscellaneous foods	Almonds, cashews, peanuts, peanut butter, nuts, tofu, soy.
Starches	Bran, oats, wheat germ, whole grain bread.
Fruit	Apricot, Gooseberry, Fig, Plum, Rhubarb.
Vegetable	Green beans, beets, chard, escarole, eggplant, chives, cabbage, leeks, mustard, okra, turnip, spinach, pumpkin, sweet potatoes, parsley, tomatoes, watercress.
Desserts	Chocolate
Drinks	Beer, chocolate, colas, tea, instant coffee.
Spice	Black olives, sesame.

*Adapted from reference 2.

the consumption of fewer carbohydrates and more fat in the diet can be useful to reduce the ostomy debt. Oxalate restriction is not necessary for patients with terminal ostomy [2].

Micronutrients

Micronutrient deficiency is common in SBS. Therefore, individualized monitoring is recommended according to the remaining anatomy of the digestive tract. **Table 5** indicates the main areas of absorption of micronutrients in the digestive system.

Medication management

The medication management of SBS in CD uses multiple strategies, such as control of inflammation, reduction of intestinal transit, a decrease of the intestinal secretion, and induction of intestinal growth. The discussion about the therapeutic approach to the CD itself will not be detailed in this review.

The use of a proton pump inhibitor should be administered intravenously initially to suppress gastric hypersecretion and reduce fluid losses. Patients with SBS usually develop hypersecretion of gastric acid during the first six months after resection.

Table 5. Micronutrient absorption sites

Stomach	Iodine.
Duodenum	Iron, Zinc, Copper, Selenium, Thiamine Folate.
Jejunum	Vitamin A, D, E, K, Thiamine, Niacin, Folate, B6, C, Iron, Zinc, Chromium.
Ileus	Vitamin B12, A, D, E, K, C, Folate.
Colon	Vitamin K.

*Adapted from reference 2

This may be associated not only with peptic disease and increased losses of intestinal fluids but also with the deactivation of pancreatic enzymes and with the reduction of the ideal pH necessary for the absorption of fats [10].

Loperamide reduces the speed of transit and can assist in the absorption process, as well as control intestinal losses. High doses may be necessary (100 mg/day are not uncommon), always administered in divided doses and 30 minutes before meals [10]. Anticholinergics are used occasionally, but the common side effect of a dry mouth is problematic as it can be mistaken for recurrent dehydration. Somatostatin and its derivatives are disappointing, as they rarely (<5%) help control water balance and can prevent adaptation [10].

However, teduglutide, an analog of the natural intestinal hormone and trophic factor GLP-2, is showing great results. It has a positive effect on the small intestine epithelium, and accumulated clinical trial data show sustained reductions in the need for parenteral nutrition in about 60% of patients (more than double that achieved in controls), perhaps with 10% of patients becoming independent of long-term parenteral nutrition after 1 year of treatment. Its price can prove to be an important limiting factor when it becomes generally prescriptive [10].

Surgical management

The options for SBS can be categorized as procedures that change motility, length, and intestinal transplantation. In the first situation, we have the Small Intestine Reverse Segment Surgery, in which an anastomosis of the small segment with an antiperistalsis orientation is performed, slowing down the digestive transit. In this procedure, a reduction in HPN of up to 50% is achieved after 60 months [2]. Other similar procedures include colon transposition, formation of intestinal valves, and enteroplasty.

In Bianchi's surgery (intestinal stretching), we divide an intestinal segment into two contiguous and isoperistaltic parts. Survival after the procedure (16-year follow-up) was 45%. Among survivors, 77% progressed with weaning from HPN [2]. The number of bowel transplants has declined dramatically in recent years, with the US being the country that most performs this procedure (58 cases in 2013). The indications are related to long-term complications of

HPN catheter-related infections, liver disease related to parenteral nutrition, failure of vascular access [2, 12].

The biggest complications of transplantation are rejection, infections, and proliferative diseases. CD is an additional risk factor for rejection in addition to the recurrence of the disease in the graft (7% in 19 months of follow-up) [2].

Few centers have data related to the survival of patients with CD in the postoperative period of intestinal transplantation. The UNOS (United Network for Organ Sharing) has published a survival rate of 79, 53, and 43% in these patients at 1, 3, and 5 years respectively [12].

Conclusion

Due to its chronic and progressive course, CD predisposes the patient to multiple surgical interventions, which can lead to SBS. Thus, the proper management of the septic condition in the postoperative period, associated with nutritional support and control of hydro electrolytic disorders plays a fundamental role in the prognosis of intestinal failure in these patients. Thus, the use of PN with a focus on the early onset of EN and the correct use of drugs to control motility and intestinal secretion contribute to an intestinal adaptation ensuring the absence of HPN. In this sense, we can still use intestinotrophic agents (eg, teduglutide) when

necessary, as well as surgical procedures and ultimately intestinal transplantation.

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No additional data are available

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Informed consent

Informed written consent obtained from the participant

Conflict of interest

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