GE – Portuguese Journal of Gastroenterology

Review Article

GE Port J Gastroenterol 2024;31:388–400
DOI: 10.1159/000538938

Received: December 18, 2023
Accepted: April 13, 2024
Published online: May 23, 2024

Chronic Intestinal Failure and Short Bowel Syndrome in Adults: The State of the Art

Francisco Vara-Luiz[a, b] Luísa Glória[c] Ivo Mendes[a] Sandra Carlos[d] Paula Guerra[e] Gonçalo Nunes[a, b] Cátia Sofia Oliveira[a] Andreia Ferreira[f] Ana Paula Santos[g] Jorge Fonseca[a, b]

[a]GENE – Artificial Feeding Team, Gastroenterology Department, Hospital Garcia de Orta, Almada, Portugal; [b]Aging Lab, Egas Moniz Center for Interdisciplinary Research (CiiEM), Egas Moniz School of Health and Science, Almada, Portugal; [c]Gastroenterology Department, Hospital Beatriz Ângelo, Loures, Portugal; [d]Surgery Department, Hospital Garcia de Orta, Almada, Portugal; [e]Pediatrics Department, Centro Hospitalar Universitário de São João, Porto, Portugal; [f]Nutrition Department, Hospital Lusíadas Lisboa, Lisboa, Portugal; [g]Pharmacy Department, Hospital Garcia de Orta, Almada, Portugal

Keywords
Intestinal failure · Home parenteral nutrition · Short bowel syndrome

Abstract

Background: Short bowel syndrome (SBS) is a devastating malabsorptive condition and the most common cause of chronic intestinal failure (CIF). During the intestinal rehabilitation process, patients may need parenteral support for months or years, parenteral nutrition (PN), or hydration/electrolyte supplementation, as a bridge for the desired enteral autonomy. ***Summary:*** Several classification criteria have been highlighted to reflect different perspectives in CIF. The management of CIF-SBS in adults is a multidisciplinary process that aims to reduce gastrointestinal secretions, slow transit, correct/prevent malnutrition, dehydration, and specific nutrient deficiencies, and prevent refeeding syndrome. The nutritional support team should have the expertise to take care of these complex patients: fluid support; oral, enteral, and PN; disease/PN-related complications; pharmacologic treatment; and surgical prevention/treatment. ***Key Messages:*** CIF-SBS is a complex disease with undesired consequences, if not adequately identified and managed. A comprehensive approach performed by a multidisciplinary team is essential to reduce PN dependence, promote enteral independence, and improve quality of life.

Falência intestinal crónica e síndrome do intestino curto em adultos: o estado de arte

Palavras Chave
Falência intestinal · Nutrição parentérica domiciliária · Síndrome do intestino curto

Resumo

Contexto: A síndrome do intestino curto (SIC) constitui uma condição clínica devastadora e mal-absortiva, sendo a causa mais comum de falência intestinal crónica (FIC). Durante o processo de reabilitação intestinal, estes

karger@karger.com
www.karger.com/pjg

Correspondence to:
Francisco Vara-Luiz, franciscovaraluiz@gmail.com

doentes poderão carecer de suporte parentérico durante meses ou anos que inclui hidratação/suplementação endovenosa e/ou nutrição parentérica (NP) como ponte para a sua progressiva autonomia e adaptação intestinal. ***Sumário:*** Diferentes classificações são elencadas e que refletem diferentes perspetivas/conceitos na FIC-SIC. A abordagem destes doentes constitui um processo multidisciplinar que tem como objetivo principal a redução das secreções gastrointestinais, reduzir o trânsito intestinal, corrigir/prevenir desnutrição, desidratação e défice nutricionais, assim como prevenir a síndrome de *refeeding*. Os centros a nível nacional devem possuir competência no tratamento de doentes com FIC, nomeadamente no manejo da fluidoterapia, nutrição oral, entérica e parentérica, complicações associadas à doença e/ou à própria nutrição parentérica, tratamento farmacológico e ainda na prevenção/tratamento cirúrgico. ***Mensagens-chave:*** A FIC-SIC constitui uma entidade complexa com consequências graves SE não for corretamente identificada/abordada. Uma abordagem holística realizada por uma equipa multidisciplinar é essencial e tem como objetivo reduzir a dependência na NP, promover adaptação intestinal e melhorar a qualidade de vida dos doentes.

Introduction

Short bowel syndrome (SBS) is a malabsorptive condition that results from the loss of intestinal length due to disease or resection [1]. SBS is the most common cause of chronic intestinal failure (CIF) [2]. Due to the major loss of digestive and absorptive surface area, general consequences of CIF include diarrhea, dehydration, electrolyte abnormalities, and weight loss. Patients need parenteral support for months or years, parenteral nutrition (PN), or hydration/electrolyte supplementation. For decades, Portuguese CIF patients have been confronted with major difficulties in receiving home parenteral nutrition (HPN) [3, 4]. In 2020, a new regulation, "Norma 017/2020" [5], set the conditions for home CIF management, and more patients are being treated in an ambulatory setting. We aimed to review the general concepts, definitions, and classifications of CIF-SBS in adults, as well as to address the multimodal treatment of these patients and disease/HPN-related complications.

Concepts, Definitions, and Classification of Intestinal Failure in Adults

Intestinal failure (IF) is defined as a reduction in gut function below the minimum necessary for absorption of macronutrients and/or water and electrolytes. Intravenous supplementation is required to maintain health, growth, and body homeostasis. The reduction in absorption that does not require intravenous supplementation is called intestinal insufficiency [2]. Several classification criteria were used [2, 6–10] to reflect the different perspectives (Tables 1, 2).

From a clinical point of view, IF definition implies the necessity of intravenous support [2]. IF should be anticipated in patients with (1) a jejunostomy/ileostomy and <200 cm of proximal small bowel, (2) <100 cm of small bowel and colon in continuity, and (3) a stoma or fistula output >1.5 L/day [7]. The need for intravenous support may depend on the effectiveness of oral nutrition/hydration, quality of oral intake, and use of specific pharmacotherapy. In borderline patients, intestinal insufficiency or IF may depend on the quality of clinical management and intestinal rehabilitation.

Multimodal Treatment of CIF-SBS and Intestinal Rehabilitation

Management of CIF-SBS aims to reduce gastrointestinal secretions, slow transit, correct/prevent malnutrition, dehydration, and specific nutrient deficiencies, and to prevent refeeding syndrome [11]. Once these early targets are achieved, progression to a stable nutritional regimen is required as part of the intestinal rehabilitation process. The need for intravenous fluid/nutrition is dictated mainly by the cause of CIF, anatomy of the SBS, and pathophysiological consequences [12].

Fluid Support and Management of Dehydration in SBS

Patients with SBS are prone to dehydration [13, 14], as they are net secretors, loose fluid, and sodium from the intestine. Since the primary deficit is not chloride, which is less well cleared from the body, a balanced electrolyte solution such as Ringer's lactate is preferred instead of saline solution [13].

Gastrointestinal losses should not dictate an increase in oral liquid intake because in SBS, this leads to fluid secretion into the proximal intestine, increasing losses. Urine output is useful for monitoring dehydration in SBS, and once an acceptable volume (20 mL/kg per 24 h) has been achieved, a transition to an oral rehydration solution (ORS) may be considered, as well as a combination of

Table 1. Functional and clinical classifications for intestinal failure

Functional classification				
Type I	Acute, short-term, and often self-limiting, as for patients after abdominal surgery requiring intravenous support for a few days			
Type II	Prolonged, often in metabolically unstable patients, usually with enteric fistulas, requiring multidisciplinary care and intravenous supplementation during weeks or months			
Type III	Chronic, in metabolically stable patients, requiring intravenous supplementation over months or years (reversible or irreversible)			
Clinical classification				
	Volume of intravenous supplementation per week, mL			
	<1,000	1,001–2,000	2,001–3,000	>3,000
Intravenous energy supplementation per week, kcal/kg				
0 (A)	A1	A2	A3	A4
1–10 (B)	B1	B2	B3	B4
11–20 (C)	C1	C2	C3	C4
>20 (D)	D1	D2	D3	D4

oral/enteral and parenteral approaches [7]. The importance of restricting the intake of low-sodium fluids, such as hypotonic fluids (e.g., water, tea, alcohol, and coffee) and hypertonic fluids (e.g., regular soda and fruit juices), should be emphasized. Instead, an ORS to enhance absorption and reduce secretion is preferred in patients with an end jejunostomy [15]. ORS is rarely needed in SBS with colon in continuity because patients usually maintain adequate hydration.

Oral Nutrition

Dietary therapy should focus on the maintenance of compensatory hyperphagia. Even small amounts of luminal nutrition stimulate intestinal adaptation and protect against liver diseases and other complications [7]. Dietary counseling should be based on patient preferences to ensure high compliance. Adjustments can be made based on the tolerance, symptoms, stool output, and weight. Due to malabsorption, dietary intake must be increased by at least 50% from the estimated needs, divided into 5–6 meals throughout the day [16]. High-energy-density foods with high salt content are recommended. Patients should use salt liberally and restrict oral fluid intake during meals.

In patients with SBS and colon in continuity, a high-carbohydrate (60%), low-fat (20%) diet with oxalate restriction (e.g., peanuts and baked beans) tend to reduce fecal calorie loss, increase energy absorption, and reduce magnesium/calcium and oxalate absorption. A high content of medium-chain triglycerides should be suggested, as well as fat restriction, as it results in steatorrhea and reduces carbohydrate fermentation [13, 17]. The fat/carbohydrate ratio in patients with end jejunostomy is less important; as enteral fat is useful owing to its energy density, they do not benefit from its restriction [18, 19].

Enteral Nutrition

Enteral nutrition (EN) should be considered, especially in those with low PN dependence, who are expected to be weaned off. Even in patients with a limited potential for complete PN weaning, EN can achieve considerable benefits [6].

Considering the altered anatomy and intra-abdominal adhesions, frequent in SBS, performing a percutaneous gastrostomy can be technically challenging. The risks and benefits must always be discussed, and a trial with a nasogastric tube should be performed.

Polymeric formulas are preferred over elemental formulas because they are less costly, less hyperosmotic, and well tolerated. However, studies suggest that both formulas are similar in terms of nutrient absorption and fluid/electrolyte loss. Continuous infusion seems to enhance the benefits and tolerance of EN. Overnight feeding improves quality of life and enables normal daily activities [20].

Table 2. Pathophysiologic and morphological classifications for intestinal failure and short bowel syndrome

Pathophsiologic classification	
Condition	Most frequent underlying disorders
SBS	• Mesenteric infarction (arterial or venous thrombosis) • Crohn's disease • Radiation enteritis • Surgical complications • Intestinal volvulus • Familial polyposis • Abdominal trauma • Intestinal angiomatosis • Necrotizing enterocolitis • Complicated intussusception • Congenital malformations
Intestinal fistula	• **Inflammatory:** Crohn's disease, diverticular disease, pancreatic disease, and radiation enteritis • **Neoplastic:** colon, ovarian and small bowel malignancies • **Iatrogenic:** operation and percutaneous drainage • **Infectious disease:** tuberculosis and actinomycosis • Trauma • Foreign body
Intestinal dysmotility	• Acute: postoperative, systemic inflammatory or neurological reaction associated with critical illnesses; Ogilvie syndrome • Chronic intestinal pseudo-obstruction
Mechanical obstruction	• Obstruction (polypoid tumors, intussusception, gallstones, foreign bodies, bezoars, feces) • Intrinsic bowel lesions (stenosis or strictures: neoplastic, inflammatory bowel disease, chemical, anastomotic) • Extrinsic lesions (abdominal adhesions: previous surgery, previous peritonitis, frozen abdomen; hernias; neoplasia: desmoid tumors, peritoneal carcinomatosis; volvulus; congenital bands)
Extensive small bowel mucosa disease	• Autoimmune enteropathy • Intestinal lymphangiectasia • Protein-losing enteropathies • Common variable immunodeficiency • Crohn's disease • Celiac disease • Radiation enteritis • Chemotherapy-related enteritis
Morphologic classification (SBS)	
Group 1	End jejunostomy (the most nutritionally dependent patient)
Group 2	Jejunocolic anastomosis
Group 3	Jejuno-ileo-colic anastomosis (the most favorable phenotype)

Home Parenteral Nutrition

Indications and Aims

HPN is indicated in patients who cannot meet their nutritional requirements despite maximal medical therapy, including oral/EN and who can be safely managed outside the hospital. It aims to support nutrition, provide hydration, and avoid electrolyte disturbance. HPN also promotes autonomy and a better quality of life, as well as intestinal rehabilitation, as part of the desired weaning off process [6].

Training and Monitoring

Before starting HPN, the patient must be metabolically stable, able to cope with HPN therapy, and have adequate social support and home environment. Patients and/or

Table 3. Components and recommendations of home parenteral nutrition

Components	Recommendations
Protein	0.8–1.4 g/kg/day (0.13–0.24 g/kg/day of nitrogen)
Energy intake	20–35 kcal/kg/day
Carbohydrates	Target: glucose (fasting) <140 mg/dL; pre-infusion/meals 100–140 mg/dL; during HPN infusion 140–180 mg/dL
Lipids	1 g/kg/week containing essential fatty acids When more than 1 g/kg/day of lipid emulsion is required, alternative emulsions to reduce the risk of liver disease (olive oil, MCT, and fish oil) should be used, which tends to be high in ω-3 PUFA and α-tocopherol and low in ω-6 PUFA and phytosterol content
Vitamins	Adjustments and supplementations as needed Evaluate baseline vitamin levels and to reevaluate them once a year
Trace elements	Adjustments and supplementations as needed Evaluate baseline vitamin levels and to reevaluate them once a year
Amino acids	No evidence for routine addiction of glutamine, cysteine, taurine
Fluids	25–35 mL/kg (2–2.5 L/day)
Electrolytes	As recommended daily intake; adjustments and supplementations as needed Regular monitoring of chloride and bicarbonate is recommended to assess acid-base balance

MCT, medium-chain triglyceride; PUFA, poly-unsaturated fatty acids.

caregivers must demonstrate self-care competency before discharge [7]. Training starts during hospitalization and aims to ensure the safe practice of HPN by teaching all aspects of infusion. Catheter care and pump use should be focused on to prevent, recognize, and effectively manage possible complications. Despite its recognized importance, there are no available guidelines for training patients/caregivers [6]. The European Society for Clinical Nutrition and Metabolism (ESPEN) encourages HPN patients to join nonprofit groups that can assist in providing education, support, and networking, which are beneficial in terms of QoL, depression scores, and catheter infections [7].

Regular contact between the nutritional support team (NST) and the patient is essential, initially every few days, then weekly, and eventually monthly. Monitoring weight, urine/stoma output, and hydration status is of utmost importance. Serum electrolytes, including sodium, potassium, chloride, bicarbonate, and renal function tests, should be measured frequently until stable and then at regular intervals, monthly to every 3 to 6 months, on a case-by-case basis. Moreover, regular monitoring of chloride and acid-base status through arterial blood samples is recommended [7]. Blood counts, liver enzymes, bilirubin, and albumin levels should also be monitored to address potential complications. Vitamins and trace elements should be measured every 6–12 months. Patients starting HPN should undergo bone mineral densitometry and measurement of markers of bone turnover, such as PTH and vitamin D, at yearly intervals. Biochemistry and anthropometry must be evaluated during all visits.

Quality of care is measured by evaluating HPN-related complications, hospital readmissions, and weight change, as well as by regular audits of the patient's quality of life. The HPN-QoL is a specific questionnaire [21] that focuses on physical, emotional, and symptomatic issues, although it has not been validated in the Portuguese population.

Components of HPN

Table 3 summarizes the components of HPN [22–28]. The adequacy of HPN volume should be assessed by 24-h urine output and serial measurements of sodium, potassium, phosphate, magnesium, and calcium levels.

Venous Catheters

Patients with HPN require long-term central venous catheter (CVC). Current guidelines recommend ultrasound-guided catheter placement in a central vein (subclavian or jugular) by an experienced physician to reduce the number of immediate and late complications [7].

Essentially, 2 types of catheters are used for HPN: cuffed tunneled central catheter (*Hickman-Broviac*) and a totally implanted port catheter (Implantofix-type). The choice between them depends on the frequency of venous access required, patient compliance, and experience of the NST [6, 7, 29]. A *Hickman-Broviac* is usually preferred,

while port catheters are reserved for patients who only need parenteral hydration, who do not use the CVC daily, or who practice sports/other activities that benefit from the CVC totally implanted under the skin.

General recommendations and precautions include [7]: (1) using a single-lumen catheter; (2) choosing the maximum necessary diameter of the catheter for the type of solute to be administered; (3) using the CVC only for the administration of PN; (4) using a perfusion pump for the solute to be administered; (5) handling of the CVC by the same person and monitored by the NST; (6) performing hand hygiene and disinfection before and after handling the CVC; (7) replacing the administration system every 24 h; and (8) flushing the CVC before and after its use with saline solution.

Weaning Perspectives/Enteral Autonomy

Virtually all patients with SBS will require PN, although more than 50% will be able to be weaned completely from PN in 5 years, in parallel with progressive enteral autonomy [10]. However, rehabilitation should be initiated as soon as possible. The probability of eliminating HPN dependence is <6% if not accomplished in the first 2 years [9]. In this matter, two principles apply: avoiding exclusive or total intravenous feeding and implementing oral/EN.

Permanent IF is expected for 100 cm or less of the small intestine in patients with end jejunostomy, 65 cm of jejunum in jejunocolic anastomosis, and 35 cm of small bowel in jejunoileal anastomosis [30]. Patients with colon in continuity and initially less dependent on HPN have generally a better prognosis [31].

HPN Complications

Tables 4 and 5 summarize the disease- and catheter-related complications of HPN [32–41].

Precautions for Orally Administered Medications

Absorption of oral medication may be impaired in patients with SBS, especially in those without the proximal jejunum. Enteric-coated and delayed-release medications may not be properly absorbed and should be avoided. When feasible, alternative routes (e.g., intravenous, subcutaneous, transdermal, and rectal) may be considered.

Pharmacologic Treatment

Antisecretory Drugs

Enterectomy is associated with gastric hypersecretion and hypergastrinemia, especially within the first 6–12 months after resection, contributing to increased intestinal fluid loss and risk of peptic ulcer disease [42]. Antisecretory drugs, including proton pump inhibitors (PPI) and histamine-2 receptor antagonists, can be used to counteract these effects. However, these medications increase the risk of small-intestinal bacterial overgrowth. The beneficial effects on stool volume and dyspeptic symptoms should be weighed against this potential risk. The duration of its beneficial effects remains unclear; however, these medications should be used cautiously beyond 6–12 months. ESPEN recommends its use, especially during the first 6 months after surgery, mainly in patients with SBS with a fecal output exceeding 2 L/day, and suggests that these drugs are also effective in reducing fecal wet weight and sodium excretion in the long-term [7, 43].

Antidiarrheal Drugs

Antidiarrheal agents, such as loperamide and codeine, are used to prolong intestinal transit time, enhance absorption, and reduce fecal wet weight and sodium excretion in patients with SBS with ostomy. Since opiate drugs have central nervous system side effects, such as sedation, and may have potential for addiction, loperamide should be preferred. Nevertheless, if necessary, combining these agents can enhance their effectiveness [44]. The use of these agents should be guided by objective measurement of their effects.

High doses of loperamide are frequently needed (reaching up to 32–64 mg/day), especially in patients with SBS without ileum, as it needs to enter the enterohepatic circulation. Although higher than the recommended label dose, loperamide is well tolerated by patients with SBS [45]. Nevertheless, side effects, such as arrhythmias, should be carefully monitored when administered at such doses. Administration 30–60 min before meals and at bedtime is often suggested, although there is no robust evidence for these recommendations.

Octreotide

Octreotide should be considered for patients experiencing severe fluid loss that cannot be effectively managed using conventional treatment. Typical candidates for this therapy include patients with SBS and high output end jejunostomy [46]. Dosage is 100–300 μg subcutaneously three times per day. Careful monitoring is required because of the potential fluid retention and possible negative influence on the intestinal rehabilitation process with prolonged use.

Antibiotics

Bloating, diarrhea, abdominal discomfort, and bowel dilation should raise suspicion for small-intestinal bacterial overgrowth, and empirical antibiotic treatment should be started accordingly. Frequently used antibiotics in this context include rifaximin, metronidazole, trimethoprim-sulfamethoxazole, and amoxicillin-clavulanic acid [47, 48].

Table 4. Disease-related complications of short bowel syndrome/intestinal failure

Complication	Pathophysiology	Management	Prevention
Intestinal failure liver disease (IFALD)	• Multifactorial condition (sepsis, intestinal anatomy, oral nutrition/EN, PN infusion modality, nutrition deficiency or excess) • Soybean-lipid emulsions in excess • Steatosis (adults) • Hepatocellular injury or cholestasis (children)	• Reduce the total lipid amount and/or decrease omega-6/omega-3 PUFA ratio • Revise potential inflammatory/infectious foci • No evidence to recommend lipid-free regimens, as well as the use of ursodeoxycholic acid, choline, taurine, or carnitine	• Identify/treat sepsis • Identify/treat sepsis • Preserve small intestine length and colon in continuity • Increase oral/enteral intake • Cycled PN with soybean oil-based lipid content less than 1 g/kg/day
Gallbladder sludge and stones	• Negligible oral intake • Intestinal remnant length less than 180 cm • Crohn's disease	• Endoscopic/surgical procedures as for the general population • Increase oral/enteral intake	• Preserve small intestine length and colon in continuity • Increase oral/enteral intake
Kidney disease and stones	• Chronic dehydration (kidney disease) • Increased absorption of oxalate, hypovolemia, hypomagnesemia and metabolic acidosis (kidney stones)	• Management as for the general population	• Monitor fluid balance and renal function* • Low-fat and low-oxalate diet* • Calcium carbonate and potassium citrate supplementation*
Bone disease	• Toxicity from aluminum contamination of the nutrition formula • Increased sensitivity to vitamin D suppressing PTH secretion • Hypercalciuria • Micronutrient deficiency (vitamin C and copper) • Vitamin A toxicity	• Supplement calcium and vitamin D as needed	• Correct metabolic acidosis when present • Periodic assessment of bone mineral density, calcium, magnesium, vitamin D and supplement as needed

EN, enteral nutrition; PN, parenteral nutrition; PUFA, poly-unsaturated fatty acid. *Especially in patients with colon in continuity.

However, routine use of antibiotics in patients with colon in continuity is not recommended because it may reduce the benefit of energy salvage due to bacterial fermentation.

Glucagon-Like Peptide-2 Analogs

In recent years, there has been growing interest in the gut endocrine system [49]. In the context of SBS, there is great interest in the use of growth factors. Targeting the glucagon-like peptide-2 (GLP-2) receptor is a promising therapeutic strategy. GLP-2 is an enteroendocrine peptide that acts through a wide variety of trophic effects to enhance mucosal growth, increase mesenteric blood flow, improve gut barrier function, slow intestinal motility, decrease gastric acid secretion, and regulate inflammatory processes [50–53]. Targeting GLP-2 receptors leads to improved absorption and reduced fluid/electrolyte loss [54].

Teduglutide was the first approved GLP-2 analog for the treatment of patients with SBS. It is a recombinant analog of GLP-2 with a longer half-life than the native peptide, allowing a daily subcutaneous injection (0.05 mg/kg/day). Typically, teduglutide is used in stable patients who cannot be weaned from PN despite all other therapeutic strategies. It has been shown to reduce PN requirements and potentially lead to complete weaning off in a subset of patients [55–57]. Additional studies are needed to determine whether intestinal adaptation due to teduglutide is sustained after discontinuation.

As this drug acts as a growth factor, it is contraindicated in patients with active or recent malignancies [58]. Screening with colonoscopy before initiating and during treatment is recommended, although the optimal timing and frequency are unknown. A suggested approach involves annual colonoscopy during the first 2 years, followed by subsequent colonoscopies at a minimum interval of 5 years [59].

Clinical experience with teduglutide suggests that it is generally well tolerated, with most adverse events being

Table 5. Disease-related complications of short bowel syndrome/intestinal failure

Complication	Pathophysiology	Management	Prevention
Catheter-related infections	• Local (catheter exit site, port pocket, subcutaneous catheter tunnel), or systemic infection • Most infections are bacterial in origin, but they can also be caused by fungi	• Preserve the catheter whenever possible • Remove in case of tunnel infections, port abscesses, septic shock, complicated infections (e.g., endocarditis), and blood stream fungal or virulent bacterial infection • Reinsertion of a new device should be postponed after systemic antibiotic therapy course is completed, as well as negative blood samples	• Aseptic technique during placement and dressing changes • Tunneled single-lumen catheters are advocated if possible • Proper catheter care and monitoring for signs of infection • No evidence of using in-line filters, routine catheters' replacement, antibiotic prophylaxis, heparin or 70% ethanol lock • Catheter locking with taurolidine appears to reduce catheter-related infections
Catheter-related thrombosis	• Procoagulant conditions • Diagnosed with computed tomography with angiography or with ultrasonography	• Anticoagulation (low molecular weight heparin, followed by vitamin K antagonists for 3–6 months) • Preserve the catheter whenever possible • Remove in case of infection, occlusion, contraindication to anticoagulation or symptom persistence despite appropriate therapy	• Ultrasound-guided catheter placement • Placement of the tip at the superior cavoatrial junction • Thromboprophylaxis with heparin/warfarin is not recommended
Catheter-related occlusion	• Usually the result of catheter thrombosis • HPN formula components (lipids and calcium-phosphate precipitates)	• Flush the catheter with saline to restore patency • Fibrinolytic agents (alteplase, urokinase) for thrombotic occlusion	• Flush the catheter with saline after PN infusion • Infusion pumps may reduce this complication

EN, enteral nutrition; PN, parenteral nutrition; PUFA, poly-unsaturated fatty acid. *Especially in patients with colon in continuity.

mild or moderate in severity. Gastrointestinal symptoms are the most reported adverse events, consistent with the underlying disease conditions and intestinal trophic actions of teduglutide [60]. Injection site reactions, stomal complications, and respiratory tract infections were also frequent.

The attractive physiological effects of GLP-2 have prompted many efforts to slow the very short half-life of the native GLP-2 peptide, enabling its use as a therapeutic agent. Longer-acting GLP-2 analogs such as glepaglutide and apraglutide are currently being studied [49]. Apraglutide is a highly selective and potent GLP-2 receptor agonist with high plasma protein binding and low systemic clearance, resulting in a longer half-life than native GLP-2 peptide and teduglutide. Glepaglutide appears to be less potent and less selective for the GLP-2 receptor than apraglutide. Some studies on apraglutide support a once-weekly subcutaneous dosing regimen, whereas studies on glepaglutide support a once- or twice-weekly subcutaneous dosing regimen, which can improve quality of life and treatment compliance [61–64].

Glucagon-Like Peptide-1 Analogs

GLP-1 analogs (e.g., exenatide, liraglutide, dulaglutide, or semaglutide) have been used for almost 2 decades in the treatment of diabetes mellitus type 2 and, recently, in obesity. Targeting the GLP-1 receptor in patients with SBS may influence proximal gut transit since GLP-1 seems to lack the intestinal trophic properties of GLP-2.

Some studies have shown a reduction in ostomy output and a reduction in PN requirements with GLP-1 analogs [65–67]. Another study evaluated the effects of continuous infusion of GLP-1, GLP-2, and a combination of both (GLP-1 and GLP-2) in adults with SBS. The authors found that all treatments significantly reduced fecal wet weight compared to the placebo. The effects of GLP-1 were less

potent than those of GLP-2, but the combination therapy was shown to have superior efficacy compared to each single agent, further supporting the rationale for a GLP-1/GLP-2 combination strategy in SBS [67].

Growth Hormone (Somatotropin)

The use of growth hormone (GH) in SBS patients showed a moderately favorable effect on intestinal wet weight loss, even though its use could be associated with significant side effects such as peripheral edema, arthralgia, and carpal tunnel syndrome. There are also concerns about the potential increased risk of diabetes mellitus and cancer [47]. The positive effects of GH have mainly been described in patients with SBS with colon in continuity. GH is approved only in the USA and its role is being replaced by GLP-2 agonists.

Clonidine

Clonidine has demonstrated some benefits in treating high output stool losses, likely due to its effects on intestinal motility and secretion [68, 69]. However, further studies are required to better understand its effectiveness.

Bile Acid Binders and Pancreatic Enzymes

Given the already diminished bile acid pool in patients with SBS, the use of bile acid sequestrants (such as cholestyramine) may exacerbate steatorrhea and fat-soluble vitamin losses and, therefore, should generally be avoided. There is still insufficient evidence supporting the efficacy of pancreatic enzyme supplementation for the treatment of SBS [7].

Surgical Prevention and Treatment of SBS

How to Avoid SBS and IF?

The role of surgery in IF often begins with prevention; therefore, early recognition of patients at a high risk for loss of critical bowel length should trigger conservative strategies [12, 70]. Operative prehabilitation of patients at risk (e.g., inflammatory bowel disease, malignancy, immunosuppression, and significant comorbidities) is indicated and aims to reduce the risk of postoperative complications. Nutritional and comorbidity optimization reduces the risk of high output stomas or the development of enterocutaneous fistulas.

In patients with Crohn's, bowel-sparing techniques (stricturoplasties) should be selected whenever possible, and wide anastomoses should be constructed to avoid stenosis recurrence. Extended bowel resection should be avoided in patients undergoing emergency surgery (ischemia or perforation). In situations of doubt regarding the viability of segments contiguous to those in the acute process, a "clip and drop" approach [11] should be chosen for damage control, laparostomy, and closure of the abdominal wall postponed until the patient is stable. This approach avoids wide resections and often recruits bowel segments with questionable vascularization in the context of shock, allowing anastomosis creation when conditions become favorable. Critically ill patients should maintain postoperative intra-abdominal pressure monitoring to prevent bowel ischemia.

When to Reoperate?

Patients with type 2 IF may be able to reestablish intestinal continuity; however, they should be assessed preoperatively, and the risks and benefits of new complications should be considered. The decision for reintervention requires knowledge of the disease origin, remanent bowel length, and other anatomic features, such as the presence of stomas, enteroatmospheric fistulas, and blind loops [71]. In this regard, Lal et al. [72] proposed a strategy that includes investigation/treatment of sepsis, assessment/optimization of nutritional status, knowledge of intestinal anatomy, and a long-term plan for each patient. This therapeutic plan was termed the "Sepsis-Nutrition-Anatomy-Plan" (SNAP), which serves as a useful guide to manage patients with type 2 IF.

The timing for reintervention should never be less than 6 months [12, 70, 71] after the last surgery. Procedure-related mortality and recurrence of intra-abdominal complications decrease when the patient is optimized and free of septic complications before the second intervention, which is often performed 9–12 months after the first [11, 73].

During this "bridge-to-surgery period," it is also important to provide psychological support. Whenever possible, it is recommended that these patients are discharged and receive ambulatory nutritional support before reintervention [11].

Preoperative evaluation requires radiological and endoscopic assessment of the entire digestive tract, including the segments distal to future anastomosis, to exclude stenosis. Abdominal/pelvic computed tomography with oral/vascular contrast is mandatory as an anatomical roadmap of segments to be anastomosed, to exclude intra-abdominal collections, and to evaluate the integrity of the abdominal wall [12]. Enterography and/or pelvic magnetic resonance imaging is indicated in patients with Crohn's disease to detect enteroenteric fistulas and perianal disease. In the presence of an ileal conduit or in patients who have undergone complex urological procedures, the urinary anatomy should be studied, as it may be beneficial to place ureteral stents preoperatively. There are indirect clinical signs that the abdomen has matured for surgery: absence of visible granulation tissue in the abdominal scars, bowel prolapse through the stoma or fistula orifice and a favorable "pinch test" (when the skin can be pinched and lifted from the underlying bowel, it means it can be easily dissected from it) [73].

Table 6. Indications for intestinal transplantation

Evidence of advanced or progressive IF-associated liver disease • Hyperbilirubinemia >4.5 mg/dL despite intravenous lipid modification strategies that persists for >2 months • Any combination of elevated serum bilirubin, reduced synthetic function (subnormal albumin or elevated international normalized ratio), and laboratory indications of portal hypertension and hypersplenism, especially low platelet count, persisting for >1 month in the absence of a confounding infectious event
Thrombosis of 3 out of 4 discrete upper body central veins (left subclavian and internal jugular, right subclavian and internal jugular) or occlusion of a brachiocephalic vein (last criterion should be evaluated in a case-by-case basis)
Life-threatening morbidity in the setting of indefinite PN dependence of either anatomical or functional cause (case-by-case basis)
Invasive intra-abdominal desmoids
Acute diffuse intestinal infarction with hepatic failure
Failure of first intestinal transplant

During the intervention, technical care should be taken to avoid postoperative complications [74]: (1) complete adhesiolysis of bowel segments; (2) repair of all desperitonization lesions; (3) avoid unnecessary additional resections; (4) prioritize meticulous and manual anastomosis; (5) avoid contact of the anastomoses with the abdominal wall; (6) remove previously placed infected/contaminated abdominal wall meshes; (7) never use a synthetic mesh for reconstruction; and (8) avoid reinterventions in suspected postoperative complications in favor of noninvasive/percutaneous procedures.

Role of Autologous Intestinal Reconstruction Surgery

In patients who reach a plateau of dependence on PN, with optimized nutritional/pharmacologic treatment and still no progression to enteral autonomy, autologous intestinal reconstruction surgery can be considered to improve intestinal absorption and facilitate the intestinal rehabilitation process [75]. Commonly performed procedures include antiperistaltic reversed segments, colonic interposition, tapering, longitudinal/spiral intestinal lengthening, serial transverse enteroplasty, and controlled tissue expansion. The main goals of autologous intestinal reconstruction surgery include [76] (1) slow intestinal transit to increase contact time between nutrients and mucosa, (2) correct short bowel stasis, (3) improve intestinal motility, and (4) increase mucosal surface area. Each procedure is designed to achieve one or several targets mentioned above and has its own indications and clinical applications, although evidence regarding which patients will benefit from these procedures and the optimal timing to perform the surgery is still scarce. The choice between the different methods should be individualized.

Indications for Intestinal Transplantation

Treatment options for irreversible CIF include lifelong HPN or intestinal transplantation (ITx) [34]. Although HPN is considered the primary treatment for CIF, early referral to intestinal rehabilitation centers with medical and surgical expertise is advised.

Four types of ITx have been described: (1) isolated bowel transplant, (2) combined liver-intestine transplant, (3) modified multivisceral transplant (stomach, jejunum, and ileum with or without the liver), and (4) multivisceral transplant (stomach, pancreas, duodenum, jejunum, and ileum with or without the liver). Classical indications that should prompt the assessment of candidacy for ITx in adults were revised in 2019 and are categorized in Table 6 [77].

Conclusion

CIF requires a comprehensive approach by a multidisciplinary team. Intestinal rehabilitation involves a multimodal treatment that includes nutritional intervention combined with medical management and, occasionally, surgical strategies that aim to reduce PN/HPN dependence, promote enteral independence, and improve quality of life.

Acknowledgments

The development of this paper was supported by Núcleo de Nutrição em Gastrenterologia, a special interest group of Sociedade Portuguesa de Gastrenterologia.

Statement of Ethics

Due to the nature of the article, ethical approval was not required.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This work was financially supported by an honoraria grant from Takeda Pharmaceuticals. The study sponsor was not involved in the study design, data collection, or data analysis.

Author Contributions

Francisco Vara-Luiz, Luísa Glória, Ivo Mendes, Sandra Carlos, Paula Guerra, Gonçalo Nunes, Cátia Oliveira, Andreia Ferreira, Ana Paula Santos, and Jorge Fonseca performed literature review, selection of studies, and writing. Luísa Glória and Jorge Fonseca conceived the study design, structured the content, and critically reviewed the manuscript. All authors approved the final version of the manuscript.

Data Availability Statement

All data analyzed during this review are included in this article. Further inquiries can be directed to the corresponding authors.

References

1 Pironi L. Definitions of intestinal failure and the short bowel syndrome. Best Pract Res Clin Gastroenterol. 2016;30(2):173–85. https://doi.org/10.1016/j.bpg.2016.02.011.
2 Pironi L, Arends J, Baxter J, Bozzetti F, Peláez RB, Cuerda C, et al. ESPEN endorsed recommendations. Definition and classification of intestinal failure in adults. Clin Nutr. 2015;34(2):171–80. https://doi.org/10.1016/j.clnu.2014.08.017.
3 Brito M, Padinha M, Carlos S, Oliveira C, Santos AP, Nunes G, et al. Long-term intestinal failure and home parenteral support: a single center experience. GE Port J Gastroenterol. 2023;30(2):127–33. https://doi.org/10.1159/000522161.
4 Silva R, Guerra P, Rocha A, Correia M, Ferreira R, Fonseca J, et al. Clinical, economic and humanistic impact of short bowel syndrome/chronic intestinal failure in Portugal (PARENTERAL study). GE Port J Gastroenterol. 2023;30(4):293–304. https://doi.org/10.1159/000526059.
5 Direção Geral de Saúde. Norma 017/2020 – Implementação da Nutrição Entérica e Parentérica no Ambulatório e Domicílio em Idade Adulta. Available from: https://normas.dgs.min-saude.pt/2020/09/25/implementacao-da-nutricao-enterica-e-parenterica-no-ambulatorio-e-domicilio-em-idade-adulta/.
6 Pironi L, Boeykens K, Bozzetti F, Joly F, Klek S, Lal S, et al. ESPEN guideline on home parenteral nutrition. Clin Nutr. 2020;39(6):1645–66. https://doi.org/10.1016/j.clnu.2020.03.005.
7 Cuerda C, Pironi L, Arends J, Bozzetti F, Gillanders L, Jeppesen PB, et al. ESPEN practical guideline: clinical nutrition in chronic intestinal failure. Clin Nutr. 2021;40(9):5196–220. https://doi.org/10.1016/j.clnu.2021.07.002.
8 Messing B, Crenn P, Beau P, Boutron-Ruault MC, Rambaud JC, Matuchansky C. Long-term survival and parenteral nutrition dependence in adult patients with the short bowel syndrome. Gastroenterology. 1999;117(5):1043–50. https://doi.org/10.1016/s0016-5085(99)70388-4.
9 Amiot A, Messing B, Corcos O, Panis Y, Joly F. Determinants of home parenteral nutrition dependence and survival of 268 patients with non-malignant short bowel syndrome. Clin Nutr. 2013;32(3):368–74. https://doi.org/10.1016/j.clnu.2012.08.007.
10 Iyer K, DiBaise JK, Rubio-Tapia A. AGA clinical practice update on management of short bowel syndrome: expert review. Clin Gastroenterol Hepatol. 2022;20(10):2185–94.e2. https://doi.org/10.1016/j.cgh.2022.05.032.
11 Klek S, Forbes A, Gabe S, Holst M, Wanten G, Irtun Ø, et al. Management of acute intestinal failure: a position paper from the European society for clinical nutrition and metabolism (ESPEN) special interest group. Clin Nutr. 2016;35(6):1209–18. https://doi.org/10.1016/j.clnu.2016.04.009.
12 O'Keefe SJD, Buchman AL, Fishbein TM, Jeejeebhoy KN, Jeppesen PB, Shaffer J. Short bowel syndrome and intestinal failure: consensus definitions and overview. Clin Gastroenterol Hepatol. 2006;4(1):6–10. https://doi.org/10.1016/j.cgh.2005.10.002.
13 Forbes A, Shaffer J. Challenges in treating short bowel syndrome. ESPEN LLL Module; 2023. Vol. 12.2.
14 Parrish CR, DiBaise JK. Short bowel syndrome in adults: part 3: hydrating the adult patient with short bowel syndrome. Pract Gastroenterol. 2015;XXXIX:10–8.
15 Ofei SY, Fuchs GJ 3rd. Principles and practice of oral rehydration. Curr Gastroenterol Rep. 2019;21(12):67. https://doi.org/10.1007/s11894-019-0734-1.
16 Crenn P, Morin MC, Joly F, Penven S, Thuillier F, Messing B. Net digestive absorption and adaptive hyperphagia in adult short bowel patients. Gut. 2004;53(9):1279–86. https://doi.org/10.1136/gut.2003.030601.
17 Jeppesen PB, Mortensen PB. The influence of a preserved colon on the absorption of medium chain fat in patients with small bowel resection. Gut. 1998;43(4):478–83. https://doi.org/10.1136/gut.43.4.478.
18 Nordgaard I, Hansen BS, Mortensen PB. Colon as a digestive organ in patients with short bowel. Lancet. 1994;343(8894):373–6. https://doi.org/10.1016/s0140-6736(94)91220-3.
19 McIntyre PB, Fitchew M, Lennard-Jones JE. Patients with a high jejunostomy do not need a special diet. Gastroenterology. 1986;91(1):25–33. https://doi.org/10.1016/0016-5085(86)90434-8.
20 Joly F, Dray X, Corcos O, Barbot L, Kapel N, Messing B. Tube feeding improves intestinal absorption in short bowel syndrome patients. Gastroenterology. 2009;136(3):824–31. https://doi.org/10.1053/j.gastro.2008.10.084.
21 Baxter JP, Fayers PM, McKinlay AW. The clinical and psychometric validation of a questionnaire to assess the quality of life of adult patients treated with long-term parenteral nutrition. JPEN J Parenter Enteral Nutr. 2010;34(2):131–42. https://doi.org/10.1177/0148607109348612.
22 American Diabetes Association. Standards of medical care in diabetes. Diabetes Care. 2011;34(Suppl ment_1):S11–61. https://doi.org/10.2337/dc11-s011.
23 Olveira G, Garcia-Luna PP, Pereira JL, Rebollo I, Garcia-Almeida JM, Serrano P, et al. Recommendations of the GARIN group for managing non-critically ill patients with diabetes or stress hyperglycaemia and artificial nutrition. Nutr Hosp. 2012;27(6):1837–49. https://doi.org/10.3305/nh.2012.27.6.6076.
24 Umpierrez GE, Hellman R, Korytkowski MT, Kosiborod M, Maynard GA, Montori VM, et al. Management of hyperglycemia in hospitalized patients in non-critical care setting: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2012;97(1):16–38. https://doi.org/10.1210/jc.2011-2098.

25 Stein TP, Marino PL, Harner RN, Schluter MD, Leskiw MJ, Black S. Linoleate and possibly linolenate deficiency in a patient on long-term intravenous nutrition at home. J Am Coll Nutr. 1983;2(3):241–7. https://doi.org/10.1080/07315724.1983.10719928.
26 Wanten GJ, Calder PC. Immune modulation by parenteral lipid emulsions. Am J Clin Nutr. 2007;85(5):1171–84. https://doi.org/10.1093/ajcn/85.5.1171.
27 Vanek VW, Borum P, Buchman A, Fessler TA, Howard L, Jeejeebhoy K, et al. A.S.P.E.N. position paper: recommendations for changes in commercially available parenteral multivitamin and multi-trace element products. Nutr Clin Pract. 2012;27(4):440–91. https://doi.org/10.1177/0884533612446706.
28 Culkin A, Gabe SM, Bjarnason I, Grimble G, Madden AM, Forbes A. A double-blind, randomized, controlled crossover trial of glutamine supplementation in home parenteral nutrition. Eur J Clin Nutr. 2008;62(5):575–83. https://doi.org/10.1038/sj.ejcn.1602754.
29 Parienti JJ, Mongardon N, Mégarbane B, Mira JP, Kalfon P, Gros A, et al. Intravascular complications of central venous catheterization by insertion site. N Engl J Med. 2015;373(13):1220–9. https://doi.org/10.1056/NEJMoa1500964.
30 Bielawska B, Allard JP. Parenteral nutrition and intestinal failure. Nutrients. 2017;9(5):466. https://doi.org/10.3390/nu9050466.
31 Gossum AV Chronic intestinal failure and home parenteral nutrition in adults: indications and outcomes. ESPEN LLL Module; 2020. Vol. 19.1.
32 Cavicchi M, Beau P, Crenn P, Degott C, Messing B. Prevalence of liver disease and contributing factors in patients receiving home parenteral nutrition for permanent intestinal failure. Ann Intern Med. 2000;132(7):525–32. https://doi.org/10.7326/0003-4819-132-7-200004040-00003.
33 Pironi L. Metabolic complications of home parenteral nutrition and indications for intestinal transplantation in chronic intestinal failure. ESPEN LLL Module. 2020. Vol. 19.4.
34 Pironi L, Labate AM, Pertkiewicz M, Przedlacki J, Tjellesen L, Staun M, et al. Prevalence of bone disease in patients on home parenteral nutrition. Clin Nutr. 2002;21:289e96.
35 Dibb M, Carlson G, Abraham A, Shaffer J, Teubner A, Lal S. OC-034 Salvage of central venous catheters in HPN catheter-related blood stream infections is safe and effective: 18 years experience from a national centre. Gut. 2012;61(Suppl 2):A14.3–5. https://doi.org/10.1136/gutjnl-2012-302514a.34.
36 Dibb M, Teubner A, Theis V, Shaffer J, Lal S. Review article: the management of long-term parenteral nutrition. Aliment Pharmacol Ther. 2013;37(6):587–603. https://doi.org/10.1111/apt.12209.
37 Liu Y, Zhang AQ, Cao L, Xia HT, Ma JJ. Taurolidine lock solutions for the pre- vention of catheter-related bloodstream infections: a systematic review and meta-analysis of randomized controlled trials. PLoS One. 2013;8(11):e79417. https://doi.org/10.1371/journal.pone.0079417.
38 Puiggros C, Cuerda C, Virgili N, Chicharro ML, Martinez C, Garde C, et al. [Catheter occlusion and venous thrombosis prevention and incidence in adult home parenteral nutrition (HPN) programme patients]. Nutr Hosp. 2012;27:256e61.
39 Leiberman D, Stevenson RP, Banu FW, Gerasimidis K, McKee RF. The incidence and management of complications of venous access in home parenteral nutrition (HPN): a 19 year longitudinal cohort series. Clin Nutr ESPEN. 2020;37:34–43. https://doi.org/10.1016/j.clnesp.2020.03.025.
40 Howard L, Ashley C. Management of complications in patients receiving home parenteral nutrition. Gastroenterology. 2003;124(6):1651–61. https://doi.org/10.1016/s0016-5085(03)00326-3.
41 van Miert C, Hill R, Jones L. Interventions for restoring patency of occluded central venous catheter lumens. Cochrane Database Syst Rev. 2012;2012(4):Cd007119. https://doi.org/10.1002/14651858.CD007119.pub2.
42 Jeppesen PB, Staun M, Tjellesen L, Mortensen PB. Effect of intravenous ranitidine and omeprazole on intestinal absorption of water, sodium, and macronutrients in patients with intestinal resection. Gut. 1998;43(6):763–9. https://doi.org/10.1136/gut.43.6.763.
43 Lakananurak N, Wall E, Catron H, Delgado A, Greif S, Herlitz J, et al. Real-world management of high stool output in patients with short bowel syndrome: an international multicenter survey. Nutrients. 2023;15(12):2763. https://doi.org/10.3390/nu15122763.
44 King RFGJ, Norton T, Hill GL. A double-blind crossover study of the effect of loperamide hydrochloride and codeine phosphate on ileostomy output. Aust N Z J Surg. 1982;52(2):121–4. https://doi.org/10.1111/j.1445-2197.1982.tb06083.x.
45 Ladefoged K, Christensen KC, Hegnhøj J, Jarnum S. Effect of a long acting somatostatin analogue SMS 201-995 on jejunostomy effluents in patients with severe short bowel syndrome. Gut. 1989;30(7):943–9. https://doi.org/10.1136/gut.30.7.943.
46 Hollanda Martins Da Rocha M, Lee ADW, Marin MLDM, Faintuch S, Mishaly A, Faintuch J. Treating short bowel syndrome with pharmacotherapy. Expet Opin Pharmacother. 2020;21(6):709–20. https://doi.org/10.1080/14656566.2020.1724959.
47 DiBaise JK, Young RJ, Vanderhoof JA. Enteric microbial flora, bacterial overgrowth, and short-bowel syndrome. Clin Gastroenterol Hepatol. 2006;4(1):11–20. https://doi.org/10.1016/j.cgh.2005.10.020.
48 Suzuki R, Brown GA, Christopher JA, Scully CCG, Congreve M. Recent developments in therapeutic peptides for the glucagon-like peptide 1 and 2 receptors. J Med Chem. 2020;63(3):905–27. https://doi.org/10.1021/acs.jmedchem.9b00835.
49 Bremholm L, Hornum M, Andersen UB, Hartmann B, Holst JJ, Jeppesen P. The effect of Glucagon-Like Peptide-2 on mesenteric blood flow and cardiac parameters in end-jejunostomy short bowel patients. Regul Pept. 2011;168(1–3):32–8. https://doi.org/10.1016/j.regpep.2011.03.003.
50 Benjamin MA, Mckay M, Yang PC, Cameron H, Perdue MH. Glucagon-like peptide-2 enhances intestinal epithelial barrier function of both transcellular and paracellular pathways in the mouse. Gut. 2000;47(1):112–9. https://doi.org/10.1136/gut.47.1.112.
51 Nakame K, Kaji T, Mukai M, Shinyama S, Matsufuji H. The protective and anti-inflammatory effects of glucagon-like peptide-2 in an experimental rat model of necrotizing enterocolitis. Peptides. 2016;75:1–7. https://doi.org/10.1016/j.peptides.2015.07.025.
52 Martin GR, Wallace LE, Sigalet DL. Glucagon-like peptide-2 induces intestinal adaptation in parenterally fed rats with short bowel syndrome. Am J Physiol Gastrointest Liver Physiol. 2004;286(6):G964–72. https://doi.org/10.1152/ajpgi.00509.2003.
53 Jeppesen PB, Lund P, Gottschalck IB, Nielsen HB, Holst JJ, Mortensen J, et al. Short bowel patients treated for two years with glucagon-like peptide 2: effects on intestinal morphology and absorption, renal function, bone and body composition, and muscle function. Gastroenterol Res Pract. 2009;2009:616054–12. https://doi.org/10.1155/2009/616054.
54 Iyer K, Kunecki M, Boullata JI, Fujioka K, Joly F, Gabe SM, et al. Independence from parenteral nutrition and intravenous fluid support during treatment with teduglutide among patients with intestinal failure associated with short bowel syndrome. Enteral Nutr. 2017;41(6):946–51. https://doi.org/10.1177/0148607116680791.
55 Jeppesen PB, Gilroy R, Pertkiewicz M, Allard JP, Messing B, O'Keefe SJ. Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome. Gut. 2011;60(7):902–14. https://doi.org/10.1136/gut.2010.218271.
56 Jeppesen PB, Pertkiewicz M, Messing B, Iyer K, Seidner DL, O'keefe SJD, et al. Teduglutide reduces need for parenteral support among patients with short bowel syndrome with intestinal failure. Gastroenterology. 2012;143(6):1473–81.e3. https://doi.org/10.1053/j.gastro.2012.09.007.
57 Pevny S, Pape UF, Elezkurtaj S, Rieger A, Jürgensen C, Blüthner E, et al. De novo development of distal jejunal and duodenal adenomas after 41 months of teduglutide treatment in a patient with short-bowel syndrome: a Case Report. JPEN J Parenter Enteral Nutr. 2021;45(3):652–6. https://doi.org/10.1002/jpen.1982.

58 Resumo das Características do Medicamento. Revestive, INN-teduglutide. Available from: https://www.ema.europa.eu/en/documents/product-information/revestive-epar-product-information_pt.pdf (accessed September, 2022).
59 Pape UF, Iyer KR, Jeppesen PB, Kunecki M, Pironi L, Schneider SM, et al. Teduglutide for the treatment of adults with intestinal failure associated with short bowel syndrome: pooled safety data from four clinical trials. Therap Adv Gastroenterol. 2020;13:1756284820905766. https://doi.org/10.1177/1756284820905766.
60 Hargrove DM, Alagarsamy S, Croston G, Laporte R, Qi S, Srinivasan K, et al. Pharmacological characterization of apraglutide, a novel long-acting peptidic glucagon-like peptide-2 agonist, for the treatment of short bowel syndrome. J Pharmacol Exp Ther. 2020;373(2):193–203. https://doi.org/10.1124/jpet.119.262238.
61 Agersnap MA, Sonne K, Knudsen KM, Knudsen CB, Berner-Hansen M. Pharmacokinetics of glepaglutide, A long-acting glucagon-like peptide-2 analogue: a study in healthy subjects. Clin Drug Investig. 2022;42(12):1093–100. https://doi.org/10.1007/s40261-022-01210-1.
62 Zhu C, Li Y. An updated overview of glucagon-like peptide-2 analog trophic therapy for short bowel syndrome in adults. J Int Med Res. 2022;50(3):3000605221086145. https://doi.org/10.1177/03000605221086145.
63 Kounatidis D, Vallianou NG, Tsilingiris D, Christodoulatos GS, Geladari E, Stratigou T, et al. Therapeutic potential of GLP-2 analogs in gastrointestinal disorders: current knowledge, nutritional aspects, and future perspectives. Curr Nutr Rep. 2022;11(4):618–42. https://doi.org/10.1007/s13668-022-00433-0.
64 Kunkel D, Basseri B, Low K, Lezcano S, Soffer EE, Conklin JL, et al. Efficacy of the glucagon-like peptide-1 agonist exenatide in the treatment of short bowel syndrome. Neuro Gastroenterol Motil. 2011;23(8):739–e328. https://doi.org/10.1111/j.1365-2982.2011.01723.x.
65 Hvistendahl M, Brandt CF, Tribler S, Naimi RM, Hartmann B, Holst JJ, et al. Effect of liraglutide treatment on jejunostomy output in patients with short bowel syndrome: an open-label pilot study. JPEN J Parenter Enteral Nutr. 2018;42(1):112–21. https://doi.org/10.1177/0148607116672265.
66 Merlo FD, Aimasso U, Ossola M, Ippolito M, Cravero L, Ponzo V, et al. Effects of treatment with liraglutide early after surgical intervention on clinical outcomes in patients with short bowel syndrome: a pilot observational "real-life" study. Nutrients. 2023;15(12):2740. https://doi.org/10.3390/nu15122740.
67 Madsen KB, Askov-Hansen C, Naimi RM, Brandt CF, Hartmann B, Holst JJ, et al. Acute effects of continuous infusions of glucagon-like peptide (GLP)-1, GLP-2 and the combination (GLP-1+GLP-2) on intestinal absorption in short bowel syndrome (SBS) patients. A placebo-controlled study. Regul Pept. 2013;184:30–9. https://doi.org/10.1016/j.regpep.2013.03.025.
68 Buchman AL, Fryer J, Wallin A, Ahn CW, Polensky S, Zaremba K. Clonidine reduces diarrhea and sodium loss in patients with proximal jejunostomy: a controlled study. JPEN J Parenter Enteral Nutr. 2006;30(6):487–91. https://doi.org/10.1177/0148607106030006487.
69 McDoniel K, Taylor B, Huey W, Eiden K, Everett S, Fleshman J, et al. Use of clonidine to decrease intestinal fluid losses in patients with high-output short-bowel syndrome. JPEN J Parenter Enteral Nutr. 2004;28(4):265–8. https://doi.org/10.1177/0148607104028004265.
70 de Vries FEE, Claessen JJM, van Hasselt-Gooijer EMS, van Ruler O, Jonkers C, Kuin W, et al. Bridging-to-Surgery in patients with type 2 intestinal failure. J Gastrointest Surg. 2021;25(6):1545–55. https://doi.org/10.1007/s11605-020-04741-0.
71 Iyer KR. Surgical management of short bowel syndrome. JPEN J Parenter Enteral Nutr. 2014;38(1 Suppl l):53S–9S. https://doi.org/10.1177/0148607114529446.
72 Lal S, Teubner A, Shaffer JL. Review article: intestinal failure. Aliment Pharmacol Ther. 2006;24(1):19–31. https://doi.org/10.1111/j.1365-2036.2006.02941.x.
73 Witte MB. Reconstructive surgery for intestinal failure. Visc Med. 2019;35(5):312–9. https://doi.org/10.1159/000503042.
74 Vaughan WG, Grosfeld JL, West K, Scherer LR, Villamizar E, Rescorla FJ. Avoidance of stomas and delayed anastomosis for bowel necrosis: the "clip and drop-back" technique. J Pediatr Surg. 1996;31(4):542–5. https://doi.org/10.1016/s0022-3468(96)90492-3.
75 Boroni G, Parolini F, Stern MV, Moglia C, Alberti D. Autologous intestinal reconstruction surgery in short bowel syndrome: which, when, and why. Front Nutr. 2022;9:861093. https://doi.org/10.3389/fnut.2022.861093.
76 Lauro A, Coletta R, Morabito A. Restoring gut physiology in short bowel patients: from bench to clinical application of autologous intestinal reconstructive procedures. Expert Rev Gastroenterol Hepatol. 2019;13(8):785–96. https://doi.org/10.1080/17474124.2019.1640600.
77 Kaufman SS, Avitzur Y, Beath SV, Ceulemans LJ, Gondolesi GE, Mazariegos GV, et al. New insights into the indications for intestinal transplantation: consensus in the year 2019. Transplantation. 2020;104(5):937–46. https://doi.org/10.1097/TP.0000000000003065.