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Definitions of intestinal failure and the short bowel syndrome

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A B S T R A C T

The European Society for Clinical Nutrition and Metabolism defined intestinal failure (IF) as "the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation is required to maintain health and/or growth". IF is classified as type 1-acute, type 2-prolonged acute and type 3-chronic IF. A short bowel syndrome (SBS) due to the intestinal malabsorption associated with a functional small intestine length of less than 200 cm is the most frequent mechanism of IF. SBS is a difficult and multifaced disease. Complications due to SBS itself and to treatments, such as long term home parenteral nutrition, can adversely affect the patient outcome. The care of SBS requires complex technologies and multidisciplinary and multiprofessional activity and expertise. Patient outcome is strongly dependent on care and support from an expert specialist team. This paper focuses on the aspects of the pathophysiology and on the complications of SBS, which are most relevant in the clinical practice, such as intestinal failure associated liver disease, renal failure, biliary and renal stones, dehydration and electrolyte depletion, magnesium deficiency and D-lactic acidosis.

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The European Society for Clinical Nutrition and Metabolism (ESPEN) has recently devised the definition and classification of intestinal failure (IF) [1] and the guidelines for chronic intestinal failure (CIF) management [2]. Furthermore, several updates and reviews on short bowel syndrome (SBS) have been published [3], prompted by the recent marketing approval in Europe and the US of an intestinal growth factor (teduglutide, a glucagon-like peptide two analogue) [4], as well as by new surgical techniques to improve bowel length and function in SBS patients [5]. The aim of this paper is to focus on the aspects of the pathophysiology and on those complications of SBS that are most relevant in the clinical practice.

Definition and classification of intestinal failure

Intestinal failure (IF) was firstly defined in 1981 by Fleming and Remington as "a reduction in the functioning gut mass below the minimal amount necessary for adequate digestion and absorption of food" [6]. In the following years, other experts further characterized this organ failure by including in the definition "the need of nutritional supplementation to maintain health and growth". Jeejeebhoy considered IF "any gut dysfunction requiring either oral or intravenous supplementation (IVS)" [7]. Jeppesen and Mortensen proposed to define IF as "only those conditions requiring intravenous supplementation", to call "intestinal insufficiency" those intestinal dysfunctions that need only enteral supplementation and define "oral failure" as the involuntary reduction of the ingestion of food [8]. Nightingale and Woodward categorized IF as "severe" when parenteral, "moderate" when enteral, and "mild" when oral nutrient/fluid supplements are needed [9]. Some Authors also included in the definition the need of micronutrients in association or alone [10]. Irving first described four mechanisms of IF, SBS, motility disorders of the bowel, SB parenchymal disease and intestinal fistula [11]. Shaffer devised a classification of IF, according to the onset modality, the metabolic characteristics and the expected outcome [12].

ESPEN recommendations, include a functional and a pathophysiological classification for both acute and chronic IF and a clinical classification of CIF [1]. IF has been defined as "the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that IVS is required to maintain health and/or growth". The panel recognized that the diagnosis and quantification of IF would be optimally done by balance study techniques comparing nutrient requirement with nutrient absorption. However, as only few centres may have the facilities for these assessments, the need of IVS was considered an indirect criterion. The ESPEN definition highlights that two criteria must be simultaneously present to diagnose IF: a "decreased absorption of macronutrients and/or water and electrolytes due to a loss of gut function" and the "need for IVS". This precludes patients receiving an IVS notwithstanding a normal intestinal absorptive function be considered as having an IF (e.g., disease-related hypophagia, anorexia nervosa, impaired swallowing or dysphagia, refusal of an otherwise effective enteral nutrition). To define the reduction of gut absorptive function that doesn't require IVS to maintain health and/or growth, the term "intestinal insufficiency" (or "intestinal deficiency" for those languages where "insufficiency" and "failure" have the same meaning) was proposed.

The "functional classification" was based on that originally proposed by Shaffer [12,13]: **type I IF**) an acute, short-term and usually self limiting condition, commonly occurring in the peri-operative setting and/or in association with critical illnesses, and requiring IVS for a few days or a few weeks; **type II IF**) a prolonged acute condition, often in metabolically unstable patients, such as those with an intra-abdominal catastrophe, enterocutaneous fistulae, or acute mesenteric ischemia, requiring complex multi-disciplinary care and IVS over periods of weeks or months; **type III IF**) a chronic condition, in metabolically stable patients, who require IVS over months or years.

The "pathophysiological classification" of IF identified five major conditions: short bowel, intestinal fistula, intestinal dysmotility, mechanical obstruction, extensive small bowel (SB) mucosal disease. In the case of a short bowel, an enterocutaneous fistula or an extensive SB disease, the primary mechanism of IF is the malabsorption of the ingested food. When an intestinal dysmotility or an intestinal mechanical obstruction occurs, IF is primarily due to the restriction of oral/enteral nutrition or total oral fasting, in order to limit or avoid the feeding-related exacerbation of digestive symptoms.

The “clinical classification” of CIF has been devised on the basis of the energy and the volume of the IVS requirement (Table 1) [1]. The clinical classification was not intended to be a “severity classification of CIF” because of the lack of simple indicators of the degree of intestinal absorption and of the number of extra-intestinal factors that can contribute to the clinical picture of the individual patient.

CIF is the rarest and less known organ failure and has been included in the 2013 Orphanet list of rare diseases [1]. In Europe, the prevalence of HPN for CIF for benign disease (absence of end stage cancer disease) has been estimated to range from 5 to 20 cases per million population, about 90% adults and 10% children. Treatment of CIF requires complex technologies as well as multidisciplinary and multi-professional activity and expertise. The outcome of patients is strongly dependent on care and support from an expert specialist team [1,2,10]. Due to the rarity of CIF, the implementation of formally structured networks linking peripheral areas with dedicated expert centers is required, because most doctors will never accumulate adequate experience for an appropriate managing of these patients [13].

Definition and classification of short bowel syndrome

In adults, normal SB length, measured from the duodenojejunal flexure, varies from about 275 cm to 850 cm, depending upon whether radiologic, surgical, or autopsy measurements are made [9].

A length of functional SB less than 200 cm is an accepted definition of short bowel in adults [9]. As the intestinal length in children is linked to the state of growth, a definition of a short bowel in absolute terms has not been devised. The need for IVS or a residual SB length of less than 25% expected for gestational age are suggested definitions of a SB in children [13]. A short bowel may be the result of extensive surgical resections or of congenital intestinal diseases [14–18]. Mesenteric ischemia, Crohn's disease, radiation enteritis, post-surgical intra-abdominal adhesions and post-operative complications are the most frequent diseases in adults, whereas children are mainly affected by intestinal volvulus, intestinal malformations and necrotizing enterocolitis [19].

The clinical feature associated with a short bowel is defined SBS [8,9,14–18]. It is essentially characterized by diarrhea, fatty stools, malnutrition and dehydration, whose severity is highly variable from patient to patient. General and localized signs and symptoms related to the systemic as well as organ and system complications, may be present. After a meal, the absorption of most of the nutrients occurs in the first 100 cm of the jejunum. Vitamin B12 and bile acids are absorbed in the last 100 cm of the ileum. Magnesium is preferentially absorbed in the distal ileum and in the proximal colon. Water and sodium absorption occurs along the entire bowel and depends on the intracellular tight junction permeability, the mechanism of sodium transportation and the intraluminal osmolarity. The tight junctions are relatively leak in the jejunum when compared to the ileum. This allows rapid fluxes of fluids and nutrients across the jejunal mucosa, making the jejunal contents become rapidly iso-osmolar. In the jejunum, sodium absorption occurs against a concentration gradient and is coupled to the absorption of glucose (solvent drag), whereas water movements are passive. Thus, the jejunal sodium and water absorption may be dependent on the sodium and glucose concentration of oral intakes as well as the intraluminal osmolarity. In the ileum, sodium absorption can take place against an electrochemical gradient even in the absence of glucose. This mechanism, combined with tighter intercellular junctions, that reduces the fluxes of water and sodium, allows a greater fluid reabsorption.

Table 1
Clinical classification of CIF [1].

IV Energy supplementation[b] (kcal/kg Body weight)	Volume of the IV supplementation[a] (ml)			
	≤1000 (1)	1001–2000 (2)	2001–3000 (3)	>3000 (4)
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

[a] Calculated as daily mean of the total volume infused per week = (volume per day of infusion × number of infusions per week)/7.

[b] Calculated as daily mean of the total energy infused per week = (energy per day of infusion × number of infusions per week)/7/Kg body weight.

Overall, it seems that the sodium fluxes, both from the lumen to plasma and vice versa, are about twice as great in the jejunum as in the ileum. Summing up the volume of ingested beverages, saliva, gastric, pancreatic and biliary secretions, about 9 liters of fluids transit the small intestine. Seven liters are reabsorbed and 2 pass the ileocecal valve and are absorbed in the colon, whose capacity for water absorption can increase up to 6 liters a day. The colon is also the place of bacteria fermentation of non absorbed carbohydrates, namely soluble fibers, from which the short chain fatty acids (SCFAs) originate. The latter is the mechanism by which the colon contributes to the intestine energy absorption, that is up to 150 kcal/day (0.62 MJ) in healthy humans and may increase up to 1000 kcal/day (about 4 MJ) in patients with intestinal malabsorption. In the terminal ileum and the proximal colon, many gastrointestinal hormones and neuromodulators, which play a key role in the control of gastrointestinal secretions, motility and intestinal growth are produced [8,9,14–18].

SBS can be categorized according to anatomical, pathophysiological and post-operative evolution criteria. According to the anatomy, three types of SBS are described: a) end-jejunostomy; b) jejuno-colic anastomosis, where the remnant jejunum is in continuity with part of the colon, most frequently left colon; c) jejuno-ileal anastomosis with ileo-cecal valve and the intact colon in continuity [8,14,17]. On the basis of the pathophysiological consequences, as well as the type and the risk of complications, SBS can be classified into two subgroups, those with intact colon or part of it in continuity and those without colon in continuity (Table 2) [8,14,17].

After a surgery procedure, the SBS evolution occurs along three stages: the acute, the adaptation and the maintenance stage [8,14,17]. The **acute stage** starts immediately after resection and generally lasts 3–4 weeks, representing a feature of type II IF, characterized by high intestinal losses and the metabolic derangement associated with major abdominal surgery. Hypergastrinaemia and gastric hypersecretion, presumably due to loss of secretion of hormonal inhibitors from the terminal ileum and colon are present, usually lasting up to six months. Careful patient management and monitoring in the hospital setting is required to avoid the potential major complications of this phase, such as dehydration and acute renal failure, electrolyte deficiencies and acid-base alterations. The **adaptation stage** usually takes place over 1–2 years. It consists in a spontaneous process, aimed to ensure a more efficient absorption of nutrients per unit length of the remaining bowel [16]. This is due partly to structural changes that increase the absorptive area and/or to functional changes that slow the gastrointestinal transit. An adaptive hyperphagia can occur. Post-operative adaptation is promoted by the presence of nutrients in the gut lumen, the pancreatic and biliary secretions and the gut hormones produced by the remnant ileum and colon. It appears to be absent or impaired in the presence of an

Table 2
Pathophysiological characteristics of the short bowel syndrome with and without a colon in continuity.

Characteristic	End-jejunostomy	Jejuno-colic or jejuno-ileal anastomosis
Structural and functional adaptation, to increase nutrient absorption	No evidence at any time after surgery	Possible up to 2 years after surgery
Gastric hypersecretion (up to 6 months after the resection)	Present	Present
Gastric emptying and SB transit	Accelerated gastric emptying for liquids Accelerated SB transit	Slowed
GI hormone secretion (PYY, GPL-1, GPL-2)	Decreased/absent	Increased
Energy absorption from microbiota SCFA production in the colon	Absent	Increased up to 1000 kcal (4.2 MJ) per day
Water and sodium absorption in the remnant SB	"Net secretion" when jejunum length <100 cm (patient may lose more fluid and sodium than ingested)	Colon adaptation can increase the absorption of water up to 6 liters and of sodium up to 800 mmol per day
Vitamin B12 and bile salt absorption	Absent	Partially conserved or absent
Magnesium absorption	Decreased	Decreased
Remnant SB length cut off for HPN weaning	>115 cm	Jejuno-colic anastomosis >60 cm Jejuno-ileal anastomosis with ICV and entire colon >35 cm

SB, small bowel; GI, gastrointestinal; SCFAs, short chain fatty acids; HPN, home parenteral nutrition; IVC, ileo-cecal valve.

end-jejunostomy [8,16]. The adaptation stage is characterized by a type III CIF, requiring IVS at home, delivered through specialized home parenteral nutrition (HPN) programs.

The SBS-associated CIF may be reversible, thus allowing patients weaned off HPN. This occurs because of the intestinal adaptation process and/or intestinal rehabilitation programs [1,8,16,20] based on pharmacological treatment and surgical procedures. CIF reversibility has been reported in about 50% in adults and up to 73% in children and it is unlikely (<10%) to occur after 2–3 years since the most recent surgery [10,21]. In adults the probability of CIF reversibility is higher when there is more than 35 cm SB with a jejuno-ileal anastomosis, the ileo-cecal valve and an intact colon, more than 60 cm SB with a jejuno-colic anastomosis or more than 115 cm SB with an end-jejunostomy [8,14,21], provided that the remaining bowel is healthy. The primary pathophysiological mechanism of CIF in the SBS is intestinal malabsorption. However, several potential "concomitant pathophysiological mechanisms" may be present in the individual patients. This makes the function of the residual bowel worse than expected on the basis of its anatomy and length, thus impairing the reversibility of CIF. This is the case of excessive fluid and electrolyte intestinal losses, a failure to develop the post-resection adaptive hyperphagia, a voluntary restriction of oral nutrient intake in an attempt to decrease the intestinal losses and a reduced oral intake because of underlying disease-related hypophagia [1,2]. In the last decade, intestinal rehabilitation programs aimed to restore and enhance intestinal function in SBS patients have been developed, consisting in surgical procedures to maximize bowel preservation at time of initial surgeries and to recruit distal unused bowel when present [5] as well as in trophic therapies to augment the endogenous process of intestinal adaptation [4]. In the **maintenance stage,** a feature of "intestinal insufficiency" may be present if the reversibility of IF occurred during the adaptation stage. Patient nutritional status and health is maintained through special diets, oral/enteral or intramuscular supplementations of nutrients and pharmacological treatments. Patients with irreversible CIF are destined to life-long HPN or to a life-saving intestinal transplantation (ITx) if a HPN-related or an underlying disease-related risk of death arises [10].

The epidemiology of SBS is not well known. The prevalence of SBS-related CIF is derived from data on the prevalence of HPN for benign disease, as SBS represent about 75% of adults and 50% of children receiving HPN in Europe. No data are available on the frequency of SBS-related intestinal insufficiency [10].

Long-term complications of short bowel syndrome

The long-term complications of SBS can be due to mechanisms related both to the gastrointestinal condition and HPN [2,8,10,14,17]. In some cases, the pathogenetic roles of the SBS and of HPN cannot be clearly separated; this is the case of IF associated liver disease (IFALD), chronic renal failure (CRF) or metabolic bone disease (MBD). Central venous catheter (CVC)-related complications are exclusively associated to HPN. Biliary and renal stones, dehydration, magnesium deficiency, electrolyte and acid-base alterations and some metabolic complications, like D-lactic acidosis and hyperammonia are mainly SBS-related (Table 3).

IFALD and gallstones

IFALD may be defined as liver injury due to factors related to IF and/or to HPN, without any other evident causes. The incidence is unknown. Cross sectional studies have reported a prevalence of alterations of the liver function test in 5–85% of patients on HPN (children > adults) [1,2,10]. Histopathology revealed the presence of cholestasis, steatosis and steatohepatitis, ductopenia and perivenular and portal fibrosis [22]. In adults and in older children, steatosis is more frequent than cholestasis, the progression to fibrosis and end stage liver failure is slow and the IFALD related-death has been reported in about 4% of total death occurred on HPN. In infants (<6 months), cholestasis is more frequent than steatosis, the progression to fibrosis and end stage liver failure is rapid and the IFALD related-death has been observed in about 16–60% of total death on HPN [10,22]. The pathogenetic factors of IFALD are grouped as HPN-related, IF-related, and systemic and/or underlying intestinal disease-related [23,24]. The risk of IFALD, especially of cholestasis, is greater in SBS with a SB remnant <50 cm, no colon in continuity with the SB, no oral diet, presence of intra-abdominal inflammation and/or SB bacterial

Table 3
Major complications of short bowel syndrome: risk factors, prevention and treatment.

	Main risk factors	Measures for prevention and treatment
Dehydration and sodium depletion	• Gastric hypersecretion (early 6 post-operative months) • Jejunostomy with <100 cm of residual small bowel ("secretors") • SBS without a colon in continuity	Optimize fluid and sodium balance to have: • urine volume >800 ml/day • urinary sodium >20 mmol/L PPI and/or ranitidine Avoid hypotonic or hypertonic beverages Oral rehydration solution
Magnesium deficiency	• Jejunostomy • Ileum and right colon resection • Fat malabsorption • Hyperaldosteronism secondary to dehydration • Impaired PTH activation and 1,25 hydroxy-vitamin D formation	Optimize fluid and sodium balance and hydration status Oral organic salt of magnesium Reduce or avoid excess lipid in the diet Oral 1-α hydroxy-cholecalciferol IV magnesium
Potassium deficiency	Jejunostomy with <50 cm of residual small bowel Hyperaldosteronism secondary to dehydration Magnesium deficiency	Optimize fluid and sodium balance and hydration status Correct magnesium deficiency Potassium supplementation (oral, IV)
Renal failure	• Dehydration • CRBSI • Nephrocalcinosis • Kidney stones	Optimize fluid and sodium balance Optimize CVC care Prevent urinary calcium oxalate formation
Calcium oxalate kidney stones	• SBS with a colon in continuity and fat malabsorption (enteric hyperoxaluria) • Pyridoxine or thiamine deficiency • Excess of ascorbic acid • Dehydration • Low urinary citrate • Low urinary magnesium	Reduce or avoid excess lipid in the diet Reduce food with high oxalate content Oral calcium at mealtime (1 gr) Oral cholestyramine Optimize fluid balance Optimize acid-base balance Optimize magnesium status Limit ascorbic acid supplementation
IFALD-cholestasis	• SBS with <50 cm of residual small bowel • SBS without colon • CRBSI episodes • Chronic intra-abdominal inflammation and/or small bowel bacterial overgrowth • Interrupted bile acid enterohepatic circulation • Oral fasting • PN-Overfeeding • IV soybean lipid emulsion >1 g/Kg/day	Avoid oral fasting Optimize CVC care Treat intra-abdominal inflammation foci Rehabilitative surgical procedures Optimize IV feeding IV soybean lipid emulsion <1 g/Kg/day and/or IV fish oil lipid emulsion
Gallstones	Prolonged oral fasting Interrupted bile acid entero-hepatic circulation Prolonged treatment with anticholinergic and narcotic drugs	Limit periods of oral fasting Limit narcotic or anticholinergic treatment Oral and/or enteral feeding as much as possible
D-lactic acid acidosis	• SBS with a colon in continuity • Carbohydrate and soluble fiber based diet • Ingestion of rapidly fermentable simple sugars • Feeding D-lactate containing food • High blood and urinary oxalate • Thiamine deficiency • Antibiotic and/or probiotic courses • Dehydration • Decreased renal function • Decreased liver function	Low carbohydrate and simple sugar diet Antibiotics active against D-lactate producing bacteria Thiamine supplementation Reduction of oxalate absorption Optimize fluid balance

SBS, short bowel syndrome; PPI, proton pump inhibitor, PTH, parathyroid hormone; IV, intravenous; CRBSI, catheter-related bloodstream infection; CVC, central venous catheter; PN, parenteral nutrition.

overgrowth, frequent occurrence of CVC-related sepsis and HPN-overfeeding, especially when a soybean-based intravenous lipid emulsion at a dose of >1 g/kg/day is provided [2,25]. Prevention and treatment consist in maintaining some oral feeding, preventing or promptly treating any infective/inflammatory foci and optimizing HPN programs [2,25]. Non-transplant surgery procedures improving or reverting the SBS-associated CIF and the reduction of the dosage of soybean lipid emulsion and/or its replacement with fish oil-based emulsions have proved to be effective in treating liver cholestasis and preventing the need of ITx due to the development of end stage liver failure [18,26].

Gall stones have been reported in 31–45% of SBS patients (with or without a colon) [8,27,28]. In a cohort of patients with CIF on HPN, the probability of developing cholelithiasis was estimated to be 6.2%, 21.2% and 38.7% at 6, 12, and 24 months, respectively [29]. SBS patients with a SB length less than 180 cm and/or an absent ileocecal valve showed the higher risk [2,8,27].

The first pathogenetic step is the formation of biliary sludge that may disappear spontaneously or evolve into gallstones, more frequently composed of calcium bilirubinate. Reduced gallbladder contractility due to the lack of cholecystokinin secretion due to oral fasting or to the use of narcotic or anticholinergic drugs, and disruption of enterohepatic circulation of bile salts due to resection and/or disease of the last 100 cm of the distal ileum, are the main factors involved in the production of a lithogenic bile [2,30,31].

Primary prevention consists in limiting the periods of oral fasting and of narcotic or anticholinergic treatment and encouraging oral and/or enteral feeding as much as possible. Prophylactic cholecystectomy at times of intestinal resection has been advocated [32] but no prospective trial has validated its usefulness. Studies on cholecystokinin administration failed to show its efficacy [2], whereas the disappearance of biliary sludge has been shown in the majority of the patients within 4 weeks after resuming oral feeding [30].

Renal disease and renal stones

Patients with a SBS, especially those with an end-jejunostomy, may have episodes of acute renal failure due to severe dehydration caused by high intestinal fluid losses, more frequently occurring in the early and in the adaptation stages of the syndrome [33]. A decrease of kidney function and the development of chronic renal failure (CRF) has been reported in patients on long term HPN for CIF. A retrospective study testing the change in glomerular filtration rate (GFR) in long-term HPN patients, showed a renal clearance decrease of 3.5% +/− 6.3% per year, a rate greater than expected from increasing age alone [34]. The number of episodes of bacteremia/fungemia was the only risk factor found to be associated with the decline of GFR. Two cross sectional studies reported a decreased GFR in 52–56% of patients on HPN [35,36]. No risk factor was found in one study [35], whereas the presence of dehydration and/or urologic or nephrologic diseases was found in the other one [36]. One more recent study [37] retrospectively compared the outcome of renal function in patients on HPN and in those who underwent ITx. The annual decline of GFR function was significantly higher in the transplanted group (−14.5%) compared to the HPN group (−2.8%). A relationship between the duration of HPN and the decline of the GFR was observed only in one study [34]. The knowledge about possible causes of CRF in HPN patients are scarce. Chronic dehydration and repeated episodes of CRBSI are suggested as primary factors [14,36]. The use of nephrotoxic medications and existing renal disease may also play a role.

Calcium oxalate (CaOx) renal stones have been shown to occur in about 25% of SBS patients with a retained colon at a median time of 30 months after the surgery [2,27]. They derive from CaOx crystallization in the collecting system. Renal colic, urinary tract infections and an obstructive uropathy with an associated risk of irreversible renal damage can develop. CaOx may also be deposited in the renal parenchyma (nephrocalcinosis) and may cause a CRF [38,39].

The primary risk factor for CaOx stones in patients with SBS is the increased colonic absorption of dietary oxalate (enteric hyperoxaluria) [38,39]. Normally, oxalate binds to calcium in the gut lumen. CaOx is not absorbed. Unabsorbed fatty acids in the colon preferentially bind to calcium and form insoluble calcium soaps, leaving oxalate unbound and available for absorption. Colonic absorption of oxalate is facilitated by increased bile salt induced colonic permeability and reduced bacterial

degradation of oxalate. Urinary oxalate can also be augmented by an increased endogenous production due to pyridoxine or thiamine deficiency and to excess of ascorbic acid.

Renal stone formation requires supersaturation of urine with calcium and oxalate and develops along three phases: nucleation, growth, and aggregation [38,39]. Dehydration and reduced urinary volume make the urine more supersaturated and nucleation more likely to occur [2]. Urinary citrate and magnesium prevent nucleation, through binding calcium and oxalate, respectively. In SBS patients, hypocitraturia due systemic metabolic acidosis and gastrointestinal bicarbonate wastage, and hypomagnesuria due to magnesium malabsorption, frequently occur.

In SBS patients without a colon in continuity the frequency of renal stones is low [27,38,39]. However, both uric acid and CaOx renal stones have been reported, being the chronic dehydration often associated with a high output stoma, the primary mechanism [2].

Prevention of renal stones primary relies on sufficient IVS to maintain normal hydration and urinary flow. Reduced intake of oxalate, correction of metabolic acidosis and supplementation with citrate and magnesium, as well as low fat diet and oral calcium supplementation (1 g of elemental calcium) at meal time should also be considered. Since in SBS patients with a colon, a diet high in carbohydrate may precipitate an episode of D-lactic acidosis, dietary fat could be partly replaced with medium-chain fatty acids, which are absorbed directly into the SB and colon. The use of cholestyramine has been reported, but has not always been successful [40]. Ascorbic acid should be supplemented with caution, as ascorbate can be metabolized to oxalate [2].

Dehydration and electrolyte depletion

Patients with SBS are at risk of fluid and electrolyte imbalance, a risk factor for renal failure [33,41], renal stones and acid-base alterations. The inadequate intestinal length impairs water and electrolyte reabsorption along the SB. In the early post-operative phase this is worsened by the presence of gastric hypersecretion [9,14,15]. SBS patients with a reduced length of jejunum ending in the stoma are those who are at particular risk. After the ingestion of either hypertonic or hypotonic fluids, many of these patients tend to secrete more sodium and fluid than they introduce in the gut lumen ("secretors") [42], because hypotonic (e.g. water, tea, coffee) fluids increase the fluid and sodium influx into the lumen and hypertonic fluids (sodas and fruit juices) stimulate fluid secretion.

SBS patients with dehydration often try to compensate they thirst by increasing oral beverage intake and this may further aggravate stomal losses and dehydration. The first treatment should be limitation of beverages or total fasting for a couple of days, to decrease intestinal losses, associated with fluid and electrolyte IVS. In order to facilitate sodium and water absorption patients are advised to sip an oral rehydration solution, a glucose-saline solution with a sodium concentration of at least 90 mmol/L that accelerates the co-transport of sodium with glucose [43,44].

The electrolyte derangement most frequently seen in SBS is sodium deficiency [8,9,14,15,17]. . At a glance, it can be assumed that about 100 mmol/L of sodium are lost with each liter of jejunostomy fluid [8,9,14,15,17]. Sodium deficiency is better detected by urinary sodium that decreases before the appearance of hyposodiaemia. A urinary sodium concentration below 10 mmol/L is a diagnostic criteria for sodium depletion. Overall, the aims of the treatment are to maintain normal hydration and a daily urine volume of at least 800 ml with a urinary sodium concentration greater than 20 mmol/L [2,8,9,14,15,17].

In SBS patients, hypokalaemia can be observed even though net intestinal loss occurs only in those with an end-jejunostomy with less than 50 cm of jejunum remnant [8]. The effluent from a jejunostomy with a longer jejunum length or a ileostomy contains approximately 15 mmol/L of potassium. A low serum potassium level is most commonly due to urinary losses of potassium associated with a secondary hyperaldosteronism elicited by dehydration and sodium depletion. Another cause of hypokalaemia may be a magnesium depletion which causes dysfunction of many of the potassium transport systems and increases renal potassium excretion; this hypokalaemia is resistant to potassium treatment but responds to magnesium replacement [2,8,9].

Hypomagnesemia

Magnesium depletion is common in SBS patients [2,9,14,15,17]. The primary pathogenetic mechanism is malabsorption due to the loss of the distal ileum and the right colon and to chelation with unabsorbed fatty acids in the bowel lumen. In patients with dehydration, an increased renal excretion of magnesium due to secondary hyperaldosteronism may also occur. Furthermore, low serum magnesium impairs the secretion and function of PTH. This may aggravate magnesium deficiency because PTH activates the renal 1,25-hydroxycholecalciferol production that stimulates intestinal and renal absorption of magnesium [2,9]. The syndrome of magnesium deficiency is characterized by neuro-muscular symptoms, cardiac arrhythmias, mental confusion and, in severe forms, convulsions [2,8,9].

Magnesium deficiency is diagnosed by a reduced serum levels and/or urinary excretion of magnesium [2]. Urinary Mg decreases before serum levels and is a more reliable indicator of Mg status, except for when hyperaldosteronism induced renal loss of magnesium occurs. Prevention and treatment consist in the correction of dehydration and in magnesium supplementation aimed to have a plasma magnesium level greater than 0.6 mmol/L (1.5 mg/dL) [9]. Oral magnesium salts at an amount 4 mmol magnesium oxide (160 mg of MgO) to a total of 12–24 mmol daily, should be the first attempt. However, this may not be successful, since magnesium oxide quickly dissociates in fluid resulting in hyperosmolar intraluminal milieu that worsens diarrhea. Organic forms, such as magnesium gluconate, dissociate slower and may be more effective [9]. A low fat diet can reduce magnesium malabsorption and oral 1-alpha hydroxy-cholecalciferol (1–9 μg daily) may improve magnesium absorption. However, in some patients IVS of magnesium is required [2,9,14].

D-lactic acidosis and other causes of mental confusion

A metabolic acidosis with increased anion-gap due to high D-lactic acid should be suspected in patients with a SBS with a colon in continuity, presenting symptoms like slurred speech, ataxia, altered mental status, psychosis, or even coma, associated with normal L-lactate serum concentration [9,45,46]. The pathogenesis depends on both the metabolic activity of colon microbiota and the individual ability to metabolize D-lactic acid [9,45,46]. In SBS patients, colonic fermentation of malabsorbed carbohydrates produces high amounts of organic acids (L- and D-lactic acid and SCFA), which lowers the luminal pH. This can promote, the growth of a high concentration of D-lactate-producing bacteria, such as *Lactobacillus fermenti*, *L. acidophilus*, and *streptococcus*. Some antibiotic and/or probiotic courses can increase the concentration of D-lactate-producing bacteria. Consequently, a high production of D-lactate may occur following the ingestion of large amounts of carbohydrates, particularly readily fermentable simple sugars. A D-lactic acidosis occurs when the metabolism and/or the excretion of D-lactate are impaired [9,45,46]. In healthy subjects, both isomers of lactate are converted to SCFA by intestinal bacteria at a rate that approximates the rate of colonic lactate production. When lactic acid-producing bacteria predominate, a decline in the number of bacteria capable of converting lactate to SCFA occurs, thus impairing one of the mechanisms of reducing fecal lactate concentration. D-lactic acid is converted to pyruvate in the kidney and in the liver by the enzyme D-2-hydroxyacid dehydrogenase. This mechanism of D-lactate metabolism may be diminished in SBS patients with compromised liver and kidney function as well as in those who have elevated concentrations of oxalate in the blood and urine, a potent inhibitor of D-2-hydroxyacid dehydrogenase. Furthermore, transient reduction of renal function, as occurs with dehydration, could impair urinary excretion of D-lactate episodically. Finally, the D-lactate serum concentrations may be increased by exogenous sources such as the ingestion of food containing D-lactate and infusion of Ringer's lactate solution [9,45,46].

The pathogenesis of neurological symptoms associated with D-lactate acidosis has not been completely clarified. It was hypothesized, that D-lactate itself is toxic to the brain or alters neurotransmitter production, but this theory has not been confirmed. It is possible that other potentially neurotoxic substances or false neurotransmitters produced in variable quantities during periods of D-lactate elevation are involved [9,45,46].

D-lactic acidosis remains sporadic and non-predictable [9,45,46]. Measurement of D-lactate concentration is not routinely available in most hospital laboratories and the diagnosis mainly relies on

clinical suspicion. Testing criteria that take into account serum bicarbonate concentration, total faecal lactate and the faecal D/L lactate ratio may become useful tools for identifying SBS patients at risk of D-lactic encephalopathy [47].

Treatment of an acute episode is based on withholding enteral intake of carbohydrate and on oral antibiotics active against D-lactate producing bacteria, such as metronidazole (500 mg, 2 times per day), vancomycin (125 mg, 4 times per day), neomycin (500 mg, 3 times per day), clindamycin (300 mg, 3 times per day) and tetracycline (500 mg, 3 times per day) [2,9,45,46]. Thiamin supplements are given to assure that adequate amounts are available for the enzyme pyruvate dehydrogenase activity that transforms pyruvate in acetil-CoA. An adequate hydration is required to optimize renal excretion of D-lactate and intravenous bicarbonate may be needed to correct the acidosis. Prevention of further episodes requires to limit substrate for bacterial production of D-lactate, limit exogenous sources of D-lactate, promote and maintain a bowel flora predominated by bacteria that do not produce D-lactate, support metabolism of D-lactate and pyruvate. Dietary treatment consists in the restriction of dietary carbohydrates, particularly simple sugars and in fractionating the total daily amount of ingested carbohydrate in frequent small meals, to limit the post-prandial peak of serum levels of D-lactate. Fermented food containing high amounts of D-lactate, such as yogurt, sauerkraut, and pickled vegetables should be avoided. Previously described measures to reduce serum oxalate should be taken. Maintaining adequate hydration and thiamin supplementation are recommended. In cases of frequent repeated episodes of D-lactate encephalopathy, a continuous regimen of rotating antibiotics may be considered in an attempt to achieve a more permanent suppression of D-lactate bacteria producers. On the contrary, patients at risk should be informed that antibiotics and probiotics prescribed for any reason could precipitate an episode of D-lactate encephalopathy [2,9,45,46].

Other rare causes of mental confusion occurring in SBS patients may be thiamine or magnesium deficiency and hyperammonemia. The latter develops because of a poor detoxification of ammonia via the urea cycle, because the short SB remnant may produce an insufficient amount of citrulline, a key amino acid to detoxify ammonia in the urea cycle. Hyperammonaemia can be corrected by giving arginine, another intermediary in the urea cycle [9].

Metabolic bone disease

Almost all the patients on long-term HPN for CIF have a MBD characterized by osteopenia, osteoporosis or osteomalacia [48]. The pathogenesis may be multifactorial. General factors, like aging and postmenopausal status, factors related to the patient's underlying illness as well as factors due to the HPN may be involved. Drugs given to treat the underlying disease, chronic inflammation, intestinal malabsorption of calcium and vitamin D deficiency are the major pathogenetic factors due to the SBS. Diagnosis and monitoring rely on bone mineral density assessment, on the measurement of serum concentration and urinary excretion of minerals, serum concentrations of vitamin D, PTH and biochemical markers of bone turnover. Prevention and treatment are based on life-style and dietary recommendations, treatment of the underlying disease related-factors and on the optimization of vitamin D nutritional status and of the HPN program. Bisphosphonates may prevent further bone demineralization [48].

Summary

CIF is the rarest and less known organ failure. SBS is the most frequent cause of CIF.

SBS is a difficult and multifaced disease. Complications due to SBS itself and to treatments, such as long term HPN, can adversely affect the patient outcome. Prevention and timely treatment of complications is a key strategy for both SBS patient survival and successful intestinal rehabilitation.

The care of SBS requires complex technologies, multidisciplinary and multiprofessional activity and expertise. Patient outcome is strongly dependent on care and support from an expert specialist team. An early referral of patients to specialized intestinal rehabilitation centers is recommended.

Practice points

- CIF in the rarest and less known organ failure.
- SBS in the most frequent cause of CIF and is a complex and multifaced disease.
- Several complications involving other organs and systems can develop in SBS patients, greatly impairing the patient outcome.
- Knowledge of SBS complications as well as their prevention and timely treatment are key issues for both patient survival and successful intestinal rehabilitation.

Research agenda

- Basic and clinical research to improve medical and surgical strategies for intestinal rehabilitation in SBS are required
- Health care system strategies to implement formally recognized networks for patients with CIF are required in order to assure equal opportunity of access to expert intestinal rehabilitation centers

Conflict of interest statement

LP has received consultancy and educational grant for Baxter, B. Braun, Fresenius Kabi and NPS/Nycomed.

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