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REVIEW ARTICLE

An overview of the current management of short-bowel syndrome in pediatric patients

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Abstract

Short-bowel syndrome (SBS) is defined as a state of malabsorption after resection or loss of a major portion of the bowel due to congenital or acquired factors. This article presents an overview on the recent management of pediatric SBS. The pediatric SBS population is very heterogeneous. The incidence of SBS is estimated to be 24.5 per 100,000 live births. The nutritional, medical, and surgical therapies available require a comprehensive evaluation. Thus, multidisciplinary intestinal rehabilitation programs (IRPs) are necessary for the management of these complex patients. The key points of focus in IRP management are hepato-protective strategies to minimize intestinal failure-associated liver disease; the aggressive prevention of catheter-related bloodstream infections; strategic nutritional supply to optimize the absorption of enteral calories; and the management and prevention of small bowel bacterial overgrowth, nephrocalcinosis, and metabolic bone disease. As the survival rate of children with SBS currently exceeds 90%, the application of small bowel transplantation has been evolving. The introduction of innovative treatments, such as combined therapy of intestinotrophic hormones, including glucagon-like peptide-2, may lead to further improvements in patients' quality of life.

Keywords Short-bowel syndrome · Intestinal failure · Intestinal rehabilitation program · Enteral autonomy

Introduction

Short-bowel syndrome (SBS) is a state of malabsorption that occurs after resection or loss of a major portion of the bowel due to congenital or acquired reasons. In SBS, the remaining bowel is unable to digest and absorb sufficient amounts of nutrients and fluid to support the patient's survival and growth. This condition is called intestinal failure (IF). SBS is the most common cause of IF in pediatric patients [1]. Since the etiology and residual bowel anatomy vary among cases, SBS patients are considered a very heterogeneous population.

SBS in children is defined by the need for parenteral nutrition (PN) for > 42–60 days after bowel resection or a residual small bowel length of < 25–30% of the expected length for age [2, 3]. A subgroup of SBS in which the remaining small bowel length is < 10–25 cm or < 10% of the expected length for age is considered ultrashort bowel [4, 5]. It is important to measure the entire bowel length at the time of resection to assess the remaining length; however, an accurate measurement of the original length may sometimes be difficult due to the bowel condition, such as in cases with dense adhesions or severe inflammation. As the bowel length increases over the first 5 years of life [6], it is important to present the residual bowel in terms of the percentage of expected bowel length for age in children.

The medical, surgical, and nutritional management of pediatric SBS is fairly complex. In clinical practice, multidisciplinary collaborative activities are essential for optimal support. We herein report an overview of the points to keep in mind when supporting SBS children.

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Ideal bowel length in children

In adults, the small bowel is said to be approximately 6–7 m, and the colon is said to be 1.5 m in length. However, the bowel length in pediatric populations varies by age. Struijs et al. proposed the ideal bowel length in children based on a large cohort study [6]. They obtained measurement data from multiracial live patients ranging in age from premature babies of 24 weeks of age to children of 5 years of age who underwent surgical procedures. The estimated ideal small bowel length (SBL) and colon length (CL) were determined with the following equations: ln [SBL (cm)] = 6.741–80.409/height (cm), CL (cm) = 0.111 × height $(cm)^{1.521}$. Height was chosen as the predictor of the patient's bowel length in their study, because, in comparison to other anthropometric data that are assessed in daily measurements, height is the most stable reference value. The bowel length calculated by this formula is very useful for assessing the expected bowel length in SBS children.

Etiology and morbidity of pediatric SBS

SBS may result from extensive resection due to congenital defects, including intestinal atresia, stenosis, gastroschisis, malrotation with volvulus, and Hirschsprung's disease. Acquired illnesses, such as necrotizing enterocolitis (NEC), traumatic injury to the small bowel, vascular thrombosis, inflammatory bowel disease, and malignancy, also lead to resection of significant loss of bowel [7–10]. The three most common causes of SBS in children are midgut volvulus, intestinal atresia, and NEC, with the vast majority of pediatric patients experiencing the onset of SBS at birth or during early infancy. The reduction of the absorptive and digestive surface area causes a decrease in digestive enzymes and transport proteins, resulting in malabsorption or IF.

Few data are available for predicting the prevalence of pediatric SBS in Japan. Given the variations in the definition of SBS among studies and heterogeneous patient backgrounds, the accurate estimation of the incidence of SBS seems difficult. Data from a large tertiary center in Canada showed that the incidence of SBS in infants was 24.5 per 100,000 live births [2]. This prevalence has been cited in many reports as a reference incidence rate for pediatric SBS.

Changes after massive bowel loss to keep in mind for optimal support

The remaining intestine undergoes adaptation, with gradual changes occurring in order to improve the absorption of adequate nutrients and fluid. This process occurs through three phases [11]. The first phase, which starts immediately after resection, is characterized by diarrhea and massive loss of fluids and electrolytes requiring total parenteral nutrition (TPN). In the second phase, several months after resection, the remaining bowel attempts to increase fluid and nutrient absorption. Gradual changes are seen, such as increasing villus height and crypt depth, thickening of the muscle layers, and compensation for the loss of absorptive digestive capacity. The structural and functional changes are more pronounced in the ileum than in the jejunum in this phase. Moderate enteral nutrition (EN) can be initiated in this phase. In the third phase, the remaining intestine adapts. The adaptation potential depends on the remaining bowel length, primary diagnosis, functional capacity of the remaining intestine, the region of bowel remaining, presence of the ileocecal valve, and presence of the colon in continuity. EN is promoted, and PN is weaned.

Notes on PN support

PN is necessary to meet the fluid and nutritional needs of SBS patients. PN is sometimes provided for several years, and some children remain on PN for life. Individual fluid requirements vary according to conditions, such as the patient's age, anatomy, amount of intestinal outputs, and other factors.

It is essential to keep in mind the possible need for long-term PN; therefore, preservation of central venous access is critical. Initially, all attempts should be made to use peripherally inserted central venous catheters (CVCs) for as long as possible in the neonatal period and early infancy. When peripheral access is exhausted, tunneled silicon CVC insertion via a larger access vessel, such as the internal jugular vein, subclavian vein, or brachiocephalic vein, may then be attempted under ultrasound-guided puncture. Open cutdown techniques should be avoided to preserve venous access [7, 12, 13].

Notes on EN support

When to initiate feeding is a critical decision. Minimal enteral feeding should be started as soon as possible and given aggressively to promote maximal bowel adaptation [14, 15]. Nutrients should be given orally whenever possible to stimulate oral motor activity and avoid feeding aversion behavior [16, 17].

Breast milk or a standard polymeric formula is recommended for initial feeding [18]. Infants under 1 year of age who show intestinal dilatation and poor motility may have an allergic reaction to the protein in the formula due to increased epithelial permeability to food antigens. Protein hydrolysate formulas are well tolerated in such cases. Amino acid formula is used to further reduce the risk of an allergic reaction [17, 19]. Solid foods may be introduced

at 4–6 months of age (corrected for gestational age). It is advised to make one change of food at a time and to offer small amounts of food frequently [14].

In infants, stool volumes of > 20 mL/kg/day may suggest the need for less aggressive advancement of EN [17]. When vomiting more than 3 times per day or exceeding 20% of the daily enteral intake is seen, it may indicate that the amount of food is still unacceptable for the patient [14]. Due to the small number and apparent heterogeneity of pediatric SBS patients, high-quality research on feeding strategies in these populations remains scarce [11]. Nutritional management for SBS children should be tailor-made and is all about balance and timing. Choosing the right food at the right time is crucial for acquiring enteral autonomy (EA).

Notes on the appropriate response to prevalent complications in SBS

Complications, such as catheter-related blood stream infections (CRBSIs), intestinal failure-associated liver disease (IFALD), small bowel bacterial overgrowth (SBBO), renal dysfunction, and metabolic bone disease (MBD), are quite prevalent and need to be kept in mind [20–24].

CRBSIs

Avoidance of recurrent CRBSIs is very important in daily CVC care. Clinically, a CRBSI is defined as a positive blood culture from the CVC and/or peripheral blood in a patient demonstrating a fever or other systemic signs of sepsis. Recurrent bacteremia can lead to a loss of vascular access and may aggravate cholestasis, eventually causing liver failure or death. Ethanol kills free bacteria in a catheter at a concentration of 15%, inhibits biofilm formation at 40%, and destroys the biofilm at 70% [25]. Chiba et al. showed the usefulness of a therapeutic ethanol lock. In a multicenter prospective study conducted in Japan, 87.5% (42/48 episodes) of patients showed a negative culture and disappearance of clinical symptoms under a daily 70% ethanol lock for 2–4 h for 7 days with optimal antibiotics [26]. In practice, it is more useful to apply the ethanol lock prophylactically, as shown by Kawano et al. The monthly instillation of 70% ethanol into the tunneled silicon CVC significantly decreased the line replacements from 4.92 to 1.72 per 1000 catheter days ($p = 0.04$) [27]. Sufficient evidence has shown that the prophylactic use of an ethanol lock reduces CRBSIs. Rahhal et al. reported a literature review of nine observational studies on the effectiveness and safety of ethanol locks compared with standard heparin locks in a pediatric IF population. The mean difference in the rate of CRBSIs was 6.27 per 1000 catheter days (95% confidence interval [CI], 4.89–7.66), favoring ethanol locks. It contributed to a 63% overall reduction in the infection rate. The mean difference shown in the catheter replacement rate per 1000 catheter days (4.56 [95% CI, 2.68–6.43]) also indicates the efficacy of periodic prophylactic ethanol lock treatments in CVC management [20].

IFALD

Although PN is a life-saving approach to nutritional management, prolonged PN can lead to a spectrum of hepatic dysfunctions, including cholestasis, steatosis, fibrosis, and cirrhosis with portal hypertension and coagulopathy [21]. IFALD is defined as a history of cholestasis with direct bilirubin ≥ 2 mg/dL for 2 consecutive weeks that is not associated with sepsis or biliary obstruction [28]. In the management of patients, it is necessary to understand that the pathogenesis of IFALD is multifactorial. It has been linked to prolonged PN dependence, phytosterols found in intravenous soybean-based lipid emulsions, sepsis, a lack of EN, and prematurity [7]. IFALD has been reported to occur in 40–60% of patients who remain on long-term PN [29, 30].

Maximum efforts should be devoted to mitigating the risk factors mentioned above. The onset of IFALD can be prevented by alternative lipid management strategies, such as lipid minimization or a change in lipid composition. The apparent therapeutic effect of Omegaven (pure fish oil emulsion, rich in omega-3 fatty acid) on cholestasis has been widely recognized since it was first reported by Boston Children's Hospital [31]. However, long-term TPN with Omegaven alone may cause a deficiency of essential fatty acids. The third-generation composite lipid emulsion SMOFlipid (containing soybean oil, medium chain triglycerides, olive oil, and fish oil) emerged in the early 2000s. Belza et al. reported the efficacy of SMOFlipid compared with traditional soybean-based lipid emulsion [32]. Patients who received SMOFlipid were less likely to reach conjugated bilirubin (CB) levels of 34 μmol/L (24% vs. 55%, $p = 0.05$) or 50 μmol/L (11.8% vs. 45%; $p = 0.028$) and did not require hepatic salvage with Omegaven (0% vs. 30%; $p = 0.014$). In addition, weight z-scores were significantly improved in patients who were receiving SMOFlipid at 3 months (− 0.932 vs. − 2.092; $p = 0.028$) and 6 months (− 0.633 vs. − 1.614; $p = 0.018$). SMOFlipid has been licensed in Europe for pediatric patients since 2009. It has also been licensed in Canada since 2013 and in the United States since 2017 but is used off-label for children. It is rapidly being accepted as the default lipid emulsion for children on long-term PN instead of the traditional soybean lipid, which is still the only lipid emulsion approved in Japan [33].

Note that sepsis has been detected as an independent predictor of the development of advanced cholestatic liver disease (odds ratio [OR] 3.23 [95% CI, 1.8–5.9]) and remains one of the leading causes of death in SBS [34]. The

avoidance of sepsis is also essential to protect the liver in SBS patients.

SBBO

The gold standard for the diagnosis of SBBO is the culturing of luminal aspirate obtained by endoscopy when growing > 10^5 CFU/mL of a bacterial species [22, 35]. However, in children, endoscopy is often not practical, so a diagnosis is often based on clinical symptoms, including abdominal distension and pain, bloating, nausea, intolerance of enteral nutrition, diarrhea, dehydration, weight loss, metabolic acidosis, and recurrent sepsis [28, 36–38].

Anatomical factors, stasis of the intestinal contents, and the use of proton pump inhibitors may contribute to the promotion of overgrowth of intestinal bacteria, leading to the development of SBBO [35]. SBBO results in mucosal inflammation, malabsorption, fat-soluble vitamin deficiency, and bacterial translocation. The decision to treat is empiric, including minimization of gastric acid suppression, the use of enteral-cycled antibiotics, and the avoidance of simple carbohydrates in the diet [38].

Gutierrez et al. assessed SBBO by quantitative cultures of duodenal aspirates obtained by upper endoscopy in 57 children who showed refractory gastrointestinal symptoms (i.e., abdominal bloating, emesis, and diarrhea or increased stoma output) [22]. They found that 70% of laboratory-confirmed SBBO cases were caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Streptococcus viridans*, or *Enterococcus* species. Antibacterial treatment is administered to patients exhibiting gastrointestinal symptoms, with particular attention to these bacterial species.

In the largest cohort study conducted to date, Belza et al. reported, based on a regression analysis, that a longer small bowel remnant was protective against the development of SBBO (OR, 0.97; 95% CI, 0.95–0.99; $p = 0.002$). Interestingly, the concentration of the Peyer patch network is thought to be more protective than the physical barrier of the ileocecal valve (ICV) [36].

We must also pay attention to the proliferation of certain *Lactobacillus* species in SBS patients with an intact colon. While undigested carbohydrates are metabolized in the colon, bacteria such as *L. fermenti* and *L. acidophilus,* which are capable of fermenting excess carbohydrates, produce D-lactic acid. Since human lactate dehydrogenase can only metabolize L-lactate, the absorbed D-lactic acid remains in the circulating blood, causing D-lactic acidosis [7, 39]. Laboratory lactic acid assays that only measure L -lactic acid will report a normal value, but acid–base values reveal anion gap metabolic acidosis. The patient may exhibit non-specific clinical symptoms, such as fatigue, lethargy, dizziness, confusion, feeling drunk, nausea, slurred speech, disorientation, ataxia, gait instability, loss of strength, inability to grasp objects, and other symptoms in the presence of unexplained acidosis. The key to therapy is to limit the amount of carbohydrates included in daily meals. Antibiotic therapy, typically metronidazole, as well as sodium or potassium acetate (bicarbonate is incompatible with the PN solution) replacement to correct the acidosis may also be useful [40].

The association between the microbiome and gut health has been a topic of interest in the field of general medicine. The application of probiotics is seen as an option to manipulate the microbiome of a patient with SBS. However, there are several concerns about septic complications from bacterial translocation or contamination of the CVC caused by the probiotic agents themselves [41, 42]. The variability in the content and quality of probiotic agents and the heterogeneity of the residual intestinal anatomy in SBS patients are other reasons underlying difficulties in evaluating probiotics. Very few studies have examined probiotics in pediatric SBS populations, and at present, research is insufficient to conclude the efficacy or appropriateness of probiotics for pediatric SBS patients [36]. From the perspective of avoiding D-lactic acid production, *L. casei*, which biochemically only produces L-lactic acid, may be clinically useful [39].

Renal dysfunction

Studies have shown that patients on long-term PN support are at risk of nephrocalcinosis. Nephrocalcinosis is defined by the deposition of mineral precipitates within the renal parenchyma [43]. The formation of nephrocalcinosis is thought to be multifactorial, including factors such as acidosis, medications such as diuretics and vitamin D supplementation, hyperoxaluria, PN, fat malabsorption, and episodes of dehydration, all of which may be present in patients with SBS [43, 44]. Kosar et al. reported that children with prolonged PN exposure, a shorter colonic remnant, and the presence of a stoma were at an increased risk of developing nephrocalcinosis [23]. Routine laboratory monitoring of creatinine is not a reliable marker for predicting the development of nephrocalcinosis; regular abdominal ultrasound surveillance is therefore important for detecting this symptom in patients with SBS. Nephrocalcinosis can be associated with long-term renal dysfunction. However, at present, whether or not nephrocalcinosis is a reliable marker of chronic renal disease in this population is unclear.

MBD

MBD is characterized by the incomplete mineralization of osteoid and consequent disturbances ranging from osteopenia to severe bone disease with pathologic fractures [45, 46]. The bulk of bone mineralization occurs in childhood and adolescence; adequate supplementation of calcium, magnesium, phosphorous, and vitamin D is thus required in SBS

patients. However, in reality, the enteral absorption of these elements is limited, and the amount of calcium and phosphorus that can be safely added to the PN solution without inducing the risk of precipitation is also limited in the clinical setting. Furthermore, potential contamination of the PN solution by aluminum must be kept in mind, as aluminum toxicity may inhibit bone mineralization [47].

Demehri et al. showed that the intestinal anatomy, such as the residual intestinal length or presence of ICV, was not significantly correlated with the bone density. The prevalence of MBD is 34–50% [24]. For the diagnosis of MBD, it is recommended that dual X-ray absorptiometry (DXA) be performed every other year once the patient reaches five years of age. MBD is deemed to be present when the bone density Z-score on DXA is ≤ -2 [28]. Bisphosphonate and glucagon-like peptide-2 (GLP-2) have been shown to improve the BMD in adult patients at risk of MBD [48], but the efficacy of these agents in pediatric patients has not yet been investigated.

Therapeutic approach with intestinotrophic agents

Careful approaches to administering EN will optimize the absorptive capacity of the residual bowel. Luminal nutrients themselves are known to play a role in stimulating the intestinal epithelial cells and promoting the secretion of trophic gut peptides by enteroendocrine cells. Among intestinotrophic hormones, GLP-2, a 33-amino acid peptide, is currently receiving the most attention.

GLP-2

GLP-2 is secreted by enteroendocrine L cells in the distal ileum and proximal colon in response to the presence of undigested luminal nutrients, especially long-chain free fatty acids and carbohydrates [49, 50]. GLP-2 increases the mucosal surface area of the gut, upregulates nutrient absorption, improves the gut-barrier function, slows motility, increases mesenteric blood flow and reduces enteric secretions; chronically, it is trophic for the small intestinal mucosa [49, 51]. Native human GLP-2 is rapidly inactivated by dipeptidyl peptidase-IV and has a short half-life of seven minutes when administered subcutaneously to humans. For this reason, a recombinant human GLP-2 analog with a longer half-life (0.897–2.99 h), teduglutide, has been used in the clinical setting.

Teduglutide is now approved in the United States, Canada, and Europe for pediatric SBS. The safety and efficacy of teduglutide was clarified with a 24-week phase III trial in 59 pediatric patients in North America and Europe [52]. Patients received 0.025 mg/kg ($n=24$) or 0.05 mg/kg ($n=26$) of teduglutide once daily subcutaneously, and the outcomes were compared with those of patients who received standard care ($n=9$). The most common adverse events were pyrexia and vomiting, but none of these incidents led to discontinuation or death. The percentage of patients achieving a $\geq 20\%$ reduction in PN volume at week 24 was significantly higher in the teduglutide 0.025-mg/kg (13/24, 54%; $p=0.05$) and teduglutide 0.05-mg/kg groups (18/26, 69%; $p=0.01$) than in the standard care group. More studies are warranted to confirm these positive effects and establish therapeutic regimens to achieve enteral autonomy when continuing the administration of GLP-2 analog administration for a prolonged duration.

In addition, translational studies on novel treatments with GLP-2, such as the application of apraglutide [53], another GLP-2 analog with an even longer half-life (30 h), and cocktail therapy with GLP-2 and epidermal growth factor (with the expectation of a synergistic effect) [54] have been conducted. These treatments have the potential to alter the nutrient absorption in human infants with SBS.

Surgical intervention techniques

Autologous bowel reconstruction is often required when the remaining intestine shows apparent dilation under the process of adaptation. The purpose of surgical intervention is to reduce the caliber of the dilated segment under the process of adaptation, to increase the bowel length, and to improve its motility, all while maintaining the maximum mucosal surface area for absorption. In addition, it is also performed to eliminate the sequelae of SBBO [36].

Longitudinal intestinal lengthening and tailoring (LILT)

In 1980, Bianchi proposed a bowel lengthening technique called LILT [55]. The dilated bowel is divided longitudinally along the midline, and two fully vascularized, isopropulsive hemiloops are created and anastomosed to each other isoperistaltically [56]. In 2012, Khalil et al. reported their 10-year experience of LILT in 19 patients. The median length of the bowel before LILT was 60 cm (range 18–140 cm), while that after LILT was 90 cm (range 37–260 cm). The residual bowel showed a 50% increase, and 88.9% (16/18) of the patients were weaned from TPN after the procedure [57]. Cases of leakage and stricture formation and the risk of injury to the intestinal blood supply have been reported [58, 59]. LILT can be a technically difficult procedure.

Serial transverse enteroplasty (STEP)

STEP was first described in 2003 by Kim et al. [60]. A GIA stapler is applied sequentially from alternating and opposite directions in a transverse, partially overlapping fashion, creating a zigzag-like channel of approximately 2–2.5 cm in diameter. A reinforcing suture at the apex of the staple lines

is routinely placed to avoid anastomotic leakage or perforation. In 2013, Jones et al. examined the clinical outcomes of 97 patients underwent STEP based on the International Serial Transverse Enteroplasty Data Registry. The median bowel length before STEP was 49 cm (range 7–200 cm), while that after STEP was 75 cm (range 17–325 cm). The residual bowel showed a 53% increase, and 55.1% (48/87) of patients were able to be weaned from TPN after the procedure [61]. Shah et al. investigated 22 SBS patients who underwent 31 different lengthening procedures and concluded that there was no marked difference in the increase in the intestinal length after LILT vs. STEP ($p = 0.74$) [62]. It is difficult to perform a simple comparison of the surgical outcomes between LILT and STEP; however, based on the relevant literature, there seems to be no marked difference between the two procedures in their efficiency with intestinal lengthening.

Spiral intestinal lengthening and tailoring (SILT)

The most recently developed lengthening technique, called SILT, was first reported in 2014 by Cserni et al. [63]. They performed the procedure on a 3-year-old girl, and 11 cm of distended bowel was lengthened to 20 cm (81.8% increase). A spiral incision is made at 45–60° to the longitudinal axis of a dilated segment, and sutures are placed where the spiral incision lines meet on the antimesenteric and mesenteric borders. The bowel is then stretched longitudinally, which requires less manipulation of the mesentery than the LILT procedure. In this procedure, the bowel does not have to be as dilated as in the LILT or STEP procedures [63]. The accumulation of case reports on SILT is required for the evaluation of its safety and feasibility for bowel lengthening in pediatric SBS patients.

Changing indications for small intestine transplantation

As noted by Ueno et al., pediatric patients should be considered for intestinal transplantation in the event of progressive IFALD, progressive loss of central vein access, and repeated life-threatening CRBSIs that require critical care [64–66]. Advances in management have led to a worldwide reduction in the number of intestinal transplants from a peak of 270 per year in 2008 to 149 per year in 2017 [67]. The need for lifelong immunosuppression and risk of significant morbidity have precluded intestinal transplantation solely to improve the quality of life (QOL) [68]. Considering the need for lifelong support, careful consideration of the pre- and post-transplant survival and QOL in individual patients is warranted concerning the application of isolated intestinal transplantations in cases of pediatric SBS.

According to the data from the international transplant registry, a total of 2010 children received 2080 intestinal transplants from 1985 to 2017. Overall, the 1- and 5-year patient/graft survival rates were 72.7%/66.1% and 57.2%/47.8%, respectively [69]. While post-transplant lympho-proliferative disorder and technical complications have contributed less to graft loss in recent years than in earlier eras, rejection remains the largest contributor to long-term graft loss at present. Evidence is emerging to support the importance of de novo donor-specific antibody (DSA) in allograft loss [70].

The latest criteria for inclusion on the waitlist for pediatric intestinal transplantation were proposed by Kaufman et al. [67]. SBS patients may be considered for intestinal transplantation when one of the following factors are present: (1) Evidence of advanced or progressive IFALD (hyper bilirubinemia > 75 μmol/L [4.5 mg/dL]) despite intravenous lipid modification strategies, which persists for > 2 months, along with any combination of elevated serum bilirubin, a reduced synthetic function as subnormal albumin or elevated INR, and laboratory indications of portal hypertension and hypersplenism; (2) Thrombosis in 3 out of 4 discrete upper body central veins or the occlusion of a brachiocephalic vein; (3) Life-threatening morbidity in the setting of indefinite PN dependence, as suggested by 2 admissions to an intensive-care unit (after initial recovery from the event resulting in IF) because of cardiorespiratory failure (mechanical ventilation or inotrope infusion) due to sepsis, or other complications of IF.

Need for multidisciplinary support with intestinal rehabilitation programs (IRPs)

In clinical practice, multidisciplinary collaborative activities are essential to respond to the diverse requirements in the daily support of SBS patients. IRPs, which were first recommended by Koehler et al. in 2000 [71], are now widely used to provide tailored care to patients with IF and their families.

What is an IRP?

The medical and nutritional management of infants or children with SBS is very complex. A multifaceted evaluation is required to interpret patient symptomology and laboratory results, adjust the enteral formula or diet composition to maximize nutrition, coordinate home therapy, and assess patient candidacy for intestinal transplantation [71]. IRPs involve pediatric surgeons, pediatric gastroenterologists, neonatologists, specialized nurses, registered dietitians, pharmacists, physiotherapists, occupational therapists, speech/feeding therapists, interventional radiologists, social workers, child life specialists, and other allied medical specialists. An IRP provides integrated multidisciplinary care,

increased discussion of patient management by involved specialists, continuity of care through various treatment interventions, close follow-up of outpatients, improved patient and family education, earlier treatment of complications, and the application of research based on accumulated patient data [72].

The Nutrition Committee of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) reported a dramatic change in outcomes with the aid of IRPs. With multidisciplinary team support, there were reductions in the number of septic events per 1000 catheter days (0.7 vs. 1.7, $p = 0.018$), mortality rate under long-term PN (33% vs. 90%, $p < 0.01$), mortality rate from end-stage liver failure (46% vs. 90%, $p < 0.01$), and mortality rate among patients waiting for transplantation (5.3% vs. 88%, $p < 0.001$) [3].

The nutrition support team (NST) concept has now been popularized throughout Japan. This concept was introduced at the end of the twentieth century in the US and Europe as an intervention to tackle malnutrition [73]. A traditional NST consists of dietitians, nurses, pharmacists, and physicians (intensivist, surgeon, gastroenterologist). In general, most NSTs conduct passive activities based on requests or consultations. They provide advice on PN or EN to in-hospital healthcare professionals; however, they cannot be involved in outpatient clinical support or handle management of the CVC. In the relevant literature, there is weak evidence to support the introduction of NSTs leading to an increased EN/PN ratio, and no convincing evidence supports the notion that NSTs lead to a reduced duration of PN or reduced complications in patients receiving PN [73, 74]. Thus, children with SBS should be actively and consistently supported under an IRP. Notably, psychological support from medical social workers or child life specialists to ease patients' or parents' concerns regarding overall treatments is essential for IRPs.

Predictors of enteral autonomy

The ultimate goal in the treatment of SBS is to promote residual bowel adaptation and reach enteral autonomy (EA) while maintaining healthy growth and development. EA is defined as freedom from PN with the maintenance of adequate hydration and growth for at least 3 months [7, 28].

There have been numerous studies on factors predicting EA. Kaji et al. noted in their study of 16 cases that a serum direct bilirubin level of < 2.0 mg/dL, the presence of ICV, and ≥ 10% of the expected normal small bowel length remaining were predictors of weaning off of PN [75].

The pediatric Intestinal Failure Consortium reported that 43% of 272 children reached EA, with a majority of the overall cohort weaned off PN in the first 24 months of life. Underlying NEC, a preserved ICV, and a longer bowel length were reported to be associated with achieving EA [1].

Fallon et al. assessed 63 patients and found the most consistent predictor to be the residual bowel length. Survivors with a neonatal residual bowel length of 50–100 cm had an 88% chance of achieving weaning from PN by 1 year of life; in contrast, the likelihood was 23% in children with a residual bowel length of < 50 cm [76]. Belza et al. mentioned that among patients with > 50% of the expected small bowel remaining, 83–100% were weaned from PN, regardless of the length of the residual colon. The median time to achieving autonomy was 1–2 years. For patients with < 50% expected small bowel remaining, the colon had a much more important role. Patients with as little as 10% of the small bowel remaining were able to achieve independence from PN if they possessed > 50% of their colon in situ. Their median time to adaptation was 4 years [77].

The Group for Improvement of Intestinal Function and Treatment (GIFT) at the Hospital for Sick Children proposed a pediatric SBS disease severity score for predicting the probability of EA [78]. They analyzed 139 patients in their IRP. Ninety-five (68%) patients achieved autonomy. Possessing > 50% of the residual small bowel (SB) (hazard ratio [HR] 2.68 [95% CI, 1.60–4.49], $p < 0.001$), an intact ICV (HR 0.61 [95% CI, 0.37–1.01], $p < 0.055$), and > 50% enteral tolerance at 6 months (HR 5.70 [95% CI, 2.77–11.74], $p < 0.001$) were positively associated with EA, while a CB level > 34 μmol/L (2 mg/dL) was negatively associated with EA (HR 0.42 [95% CI, 0.27–0.66], $p < 0.001$). A severity score was created by weighting the coefficients of the aforementioned parameters using a Cox proportional hazards model. The estimated scoring was as follows: SB length > 50% (2 points), ICV intact (1 point), CB < 34 μmol/L (2.0 mg/dL) (2 points), and EN > 50% (3 points) for a maximum score of 8 points. Score cut-off values were determined by a receiver operating curve, and then patients with scores of 6–8 (97.1% [68/70] achieved EA) were defined as the mild severity group; patients with scores of 3–5 (52.9% [18/34] achieved EA) were defined as the moderate group; and patients with scores of 0–2 (25.7% [9/35] achieved EA) were defined as the severe group. This scoring system may help predict individual prognoses in this population.

Where we are now?

The survival rate of children with SBS has improved to > 90% with the establishment of multidisciplinary support under IRPs, including hepatoprotective strategies and aggressive prevention of CRBSIs [3, 5, 79]. According to a report from the Center for Advanced Intestinal Rehabilitation (CAIR) group at Boston Children's Hospital, a cohort of 70 patients with neonatal-onset SBS who were followed for

10–19 years under IRP management showed 0% mortality, with 76% of the patients achieving EA, and 94% remaining transplant-free. In this cohort 98% of the patients attended school or graduated from secondary education [28]. As Gold et al. mentioned, the management of septic events during the first year may contribute to a reduction in poor working memory and visual-motor integration skills at school age [80]. It is necessary to provide optimal care early in life to optimize the future neurocognitive development of our patients. As the long-term survival of pediatric patients is realized, problems regarding appropriate support systems for cases transitioning to adulthood may arise.

Conclusion

The outcomes of pediatric SBS patients have improved over the years. A majority of children with SBS are now able to be weaned from PN. A decline in CRBSIs, reduction in PN hepatotoxicity, optimal EN supply, improvement of medical and surgical management, and coordinated, comprehensive care delivered by multidisciplinary IRPs have all been important advances supporting the management of pediatric SBS. The indications for being added to the list for intestinal transplantation are changing with time. Innovative treatment, such as trophic peptides, may lead to further improvement of the QOL of these patients.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest in association with the present study.

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