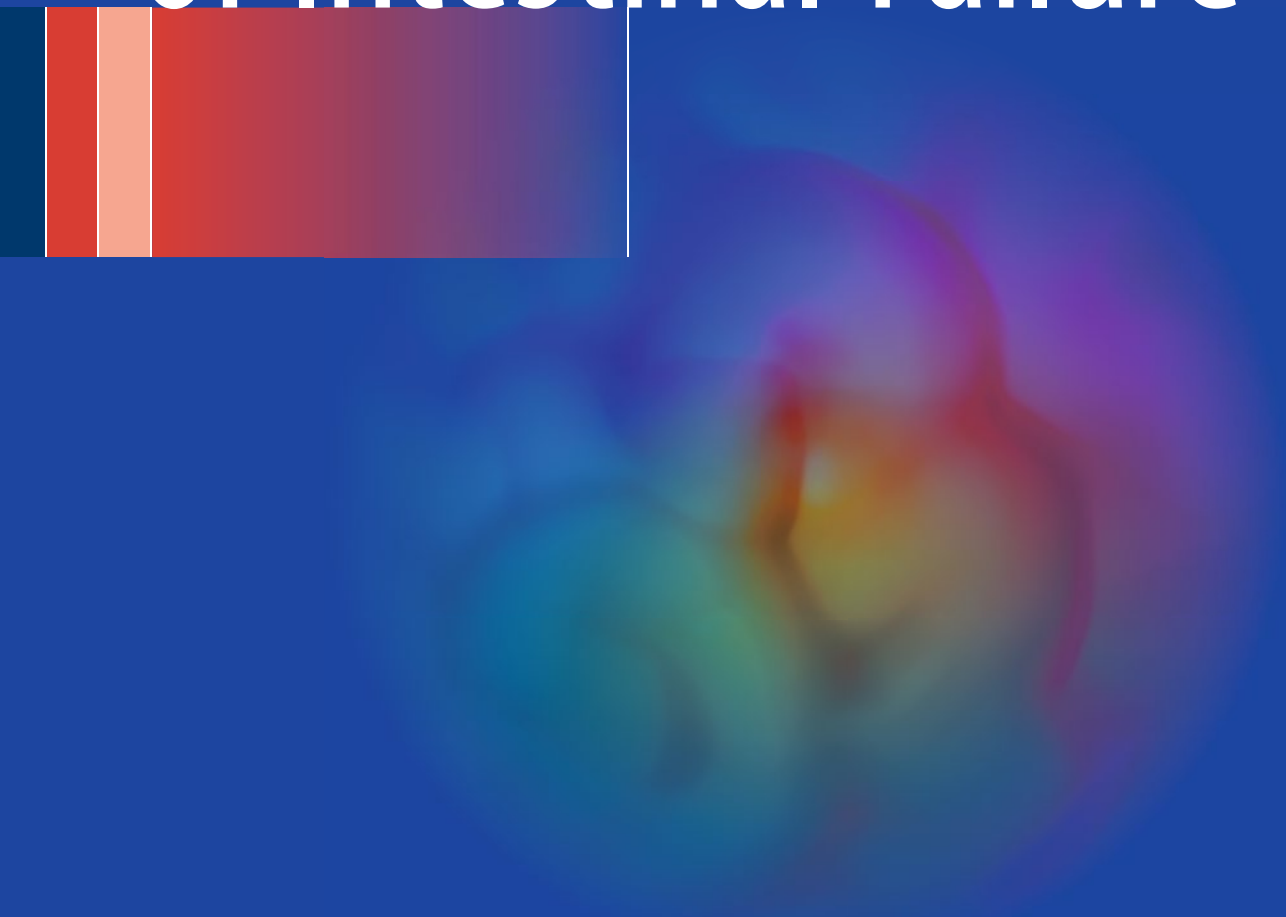
Risto J. Rintala
Mikko Pakarinen
Tomas Wester *Editors*

Current Concepts of Intestinal Failure



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Editors
Risto J. Rintala
Children's Hospital
Helsinki University Central Hospital
HUS Helsinki
Finland

Mikko Pakarinen
Children's Hospital
Helsinki University Central Hospital
HUS Helsinki
Finland

Tomas Wester
Department of Pediatric Surgery
Karolinska University Hospital
Stockholm
Sweden

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Preface

Intestinal failure in children carries a significant morbidity and mortality as well as social and economical burden. Intestinal failure can be defined as the reduction of gut function below the minimum necessary for the absorption of nutrients, such that intravenous supplementation is required to maintain health and growth. Intestinal failure in children is usually caused by three major conditions: short bowel, intestinal dysmotility, or extensive small bowel mucosal disease. The prevalence of intestinal failure remains unclear because the definitions used in different populations are variable. The estimated prevalences range between 2 and 13 per million children.

In children the intestinal length is related to the age of the child; therefore, a definition of a short bowel in absolute terms cannot be devised. The need for intravenous supplementation of nutrients and a residual small bowel length of less than 25 % expected for gestational age are suggested definitions of a short bowel in children. The main causes of short bowel in children are gastroschisis, midgut volvulus, bowel atresias, and necrotizing enterocolitis.

In addition to short bowel, intestinal failure may be due to congenital enteropathy, such as microvillus inclusion disease, and intestinal neuromuscular disorder, such as total bowel Hirschsprung's disease or intestinal pseudo-obstruction, which are associated with diminished effective absorptive small bowel.

The management of intestinal failure in children has evolved enormously during the last decades. The morbidity has decreased and the survival increased markedly. Since the 1980s the development of parenteral nutrition technology and the use of home parenteral nutrition have increased the safety of long-term parenteral administration of nutrients. The composition of parenteral nutrition formulas has evolved decreasing the metabolic complications that were very common especially in the newborn and infant population of intestinal failure patients. Intestinal failure-associated liver disease that along with septic complications of parenteral nutrition was the major complication threatening the life of intestinal failure patients has become less common and treatable by adjusting the intake and composition of parenteral fat. The central lines used for parenteral nutrition incorporate today chemical locks such as ethanol lock that protect the catheters from bacterial colonization and decrease the occurrence of catheter-related septic episodes.

Until recently, there has been less evolution in the medical treatment of intestinal failure. There are very few medications that significantly improve intestinal motility in the long term; moreover, their effects are commonly

unpredictable. Most patients require antibiotics regularly to control bacterial overgrowth episodes, but their use is associated with development of bacterial resistance. Teduglutide, a recombinant analog of glucagon-like peptide-2, is the first and a promising targeted therapeutic agent to treat short bowel-associated intestinal failure. It has been shown to reduce the requirement of parenteral nutrition significantly.

Surgical management of intestinal failure has been revolutionized by the development of autologous intestinal reconstruction techniques. Longitudinal intestinal lengthening procedure and serial transverse enteroplasty both increase the possibility of weaning off parenteral nutrition. In general, PN requirement decreases in the great majority of patients, while around half of children achieve enteral autonomy during the first two postoperative years.

Intestinal transplantation is an acceptable therapeutic option for patients with intestinal failure, but it is still reserved for patients who develop severe and life-threatening complications despite standard therapies or those who are not able to maintain a good quality of life. There has been a marked improvement in graft survival rates, especially for intestine alone grafts, over the past two decades.

Intestinal failure in children is a multifaceted condition that requires contributions of several medical and allied health professionals for hospital care and support at home. Therefore, the formation of a multidisciplinary intestinal rehabilitation team is vital to achieve optimal results. The team should include competent professionals in surgery, gastroenterology, and nutrition, a dietician, and staff experienced in handling central venous catheters and nutrient infusions. Special consideration should be given to the psychosocial support of the family during the whole treatment period.

This book has been compiled to summarize current knowledge on intestinal failure. The chapters are written by international experts in the field. The size of the book is kept compact to allow easy reading and timely and rapid updating of the content.

Helsinki, Finland — Risto J. Rintala
Mikko Pakarinen
Stockholm, Sweden — Tomas Wester

Contents

Intestinal Failure in Children

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Olivier Goulet, Florence Lacaille,
and Cécile Lambe

Abbreviations

AABF	Amino acid-based formulas
CRS	Catheter-related sepsis
CLD	Cholestatic liver disease
CIPOS	Chronic intestinal pseudo-obstruction syndrome
(CSD)	Congenital sodium diarrhea
CDED	Congenital diseases of enterocyte development
CTF	Continuous tube feeding
ETF	Enteral tube feeding
EGF	Epidermal growth factor
EFA	Essential fatty acid
GI	Gastrointestinal
GLP-2	Glucagon-like peptide 2
HM	Human milk
ICV	Ileocecal valve
IGF-1	Insulin-like growth factor-1
IF	Intestinal failure
IFALD	Intestinal failure-associated liver disease
ITx	Intestinal transplantation
ILE	Intravenous lipid emulsions
LOT	Ligament of Treitz
LILT	Longitudinal intestinal lengthening and tailoring
MCT	Medium-chain triglyceride
MVID	Microvillus inclusion disease
OF	Oral feeding
PN	Parenteral nutrition
PUFA	Polyunsaturated fatty acid
rhGH	Recombinant human growth hormone
STEP	Serial transverse enteroplasty technique
SBS	Short bowel syndrome
SCFA	Short-chain fatty acid
SIBO	Small intestinal bacterial overgrowth
TIA	Total intestinal aganglionosis
TE	Tufting enteropathy

Intestinal failure (IF) may be defined as a critical reduction of the gut mass or its function below the minimum needed to absorb nutrients and fluids required for adequate growth in children and weight maintenance in adults [1]. Severe malabsorption results in the need for life-saving artificial nutrition usually provided through a parenteral route. IF may be reversible or irreversible, depending on a number of factors such as the underlying diagnosis and also on the treatment used to develop or restore intestinal capacity. Severe and even irreversible IF in children remains a challenge. Because IF is relatively rare,

O. Goulet, MD, PhD (✉) • F. Lacaille, MD
C. Lambe, MD
Division of Pediatric Gastroenterology-Hepatology-Nutrition, National Reference Center for Rare Digestive Diseases, Pediatric Intestinal Failure Rehabilitation Center, Hôpital Necker-Enfants Malades, University Paris Descartes, Paris, France
e-mail: olivier.goulet@nck.aphp.fr

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there is not enough data to provide the scientific foundation needed to form treatment guidelines or for the creation of gold standards for the care of such patients. In clinical practice, intestinal sufficiency is indirectly measured by the percentage of parenteral nutrition (PN) required for growth. Other indicators such as residual bowel length measured at final surgery and serum citrulline, though helpful, have not proven to be highly reliable prognostic factors in children with short bowel syndrome (SBS) [2]. Therefore, PN requirements remain the best measure of the degree of intestinal sufficiency in this setting.

Due to technical refinements and steady advances in the development of highly sophisticated nutrient solutions consisting of optimal combinations of macronutrients and micronutrients, PN has became a safe feeding technique and continues to play an important role in patient management. However, some complications, such as catheter-related sepsis (CRS) and cholestasis, still occur at high incidence, particularly in neonates even during short course of PN [3–5]. Moreover, IF that requires long-term PN may be associated with various complications including CRS, growth failure, metabolic disorders, and bone disease. Cholestatic liver disease (CLD) was rapidly identified as one of the limiting factors of long-term IF management and may lead to the so-called nutritional failure which is considered as a major indication for intestinal transplantation or combined liver-intestinal transplantation. According to the current long-term graft and patient survival following intestinal transplantation (ITx), IF alone may be a debatable indication for ITx, whereas nutritional failure remains a clear indication [6].

Causes of Intestinal Failure

In developed countries, pediatric IF is most commonly due to congenital or neonatal intestinal diseases that can be divided into three groups: (i) disorders with a reduced intestinal length and consequently reduced absorptive surface, such as in SBS; (ii) disorders related to an abnormal development of the intestinal mucosa such as congenital diseases of enterocyte development (CDED); and (iii) disorders with an intact mucosal surface but with extensive motility dysfunction such as extensive intestinal pseudo-obstructions (CIPOS) or extensive aganglionosis in Hirschsprung disease (Table 1.1). Intestinal atresia as well as necrotizing enterocolitis (NEC) or gastroschisis may be associated with severe motility disorders and hence often result in more serious IF [7].

Short Bowel Syndrome

Definition and Etiology

SBS is the leading cause of pediatric IF. It is a disorder characterized by a compromised bowel absorptive capacity due to a severely reduced mucosal surface resulting in diarrhea, water-electrolyte imbalance, and malnutrition. SBS usually follows extensive surgical resection leaving the SB length below a critical value for adequate nutritional supply [6]. At birth, term-neonates have a SB length of approximately 250 cm, and their intestines lengthen substantially during the first year of life. Preterm infants have a greater potential for bowel growth [8].

The cut-off length for SBS is related to a number of factors. In general SBS occurs after a massive resection leaving less than 40 cm of viable small bowel; nevertheless, a residual bowel length of only 15–40 cm has been associated with bowel adaptation, intestinal autonomy, and PN weaning [9–13]. Important factors determine SBS prognosis: the underlying diagnosis, the type of segments preserved, a long-term stoma *versus* a primary anastomosis, the presence of the ileocecal valve (ICV), as well as the age of the patient at the time of surgery [9–13]. Other factors are relevant to the development of SBS such as the functionality of the residual bowel, especially the motility disorders [11].

In children the conditions most commonly leading to extensive small bowel resections are necrotizing enterocolitis, midgut volvulus, gastroschisis, intestinal atresia, and extensive aganglionosis, the last one leading to SBS without functioning colon (Table 1.1 and Fig. 1.1).

Table 1.1 Liver disease-related factors

Patient and intestinal failure-related factors
Prematurity and low birth weight
Lack of enteral feeding
Total parenteral nutrition
Disruption of enterohepatic biliary acid cycle
Proximal stoma, *ileal resection*
Intestinal stasis and bacterial overgrowth
Obstruction, *dysmotility*, *lack of ileocecal valve*, *over-tube feeding*
Parenteral nutrition-related factors
Duration of PN
Recurrent catheter-related sepsis
Unadapted protein-energy delivery
Excessive or unadapted amino acid intake
Continuous versus cyclic infusion
Excessive glucose intake
Unappropriate use of lipid emulsion
Phytosterols
Lipoperoxidation
Excess of omega-6 fatty acids
Essential fatty acid deficiency
Potential toxic components of PN
Iron
Aluminum
Chromium
Manganese
Deficiencies
Taurine
Chlorine

Management of SBS

Bowel adaptation after small intestine resection is a physiological process [14]. The management of SBS aims at promoting small bowel adaptation and villous hyperplasia by using as much of the gastrointestinal tract (GI) by oral feeding (OF) or enteral tube feeding (ETF) and by promoting normal somatic growth with PN.

The GI tract should be used for feeding as it is the most physiological and safest way to provide nutrition. However, PN should not be stopped until adequate intake and growth can be achieved with OF and/or ETF alone. The optimal strategy for enteral feeding, OF versus ETF and continuous versus bolus, remains a matter of debate [14]. The advantages of OF allow the maintenance of sucking and swallowing functions along with the interest and enjoyment associated with eating, thus helping to prevent eating disorders. It is important to point that OF promotes the release of epidermal growth factor (EGF) from salivary glands and increases GI secretion of trophic factors [15]. Sialoadenectomy in animals significantly attenuates ileal villus height, total protein, and DNA content after small bowel resection that is reversed by the administration of both systemic and oral EGF [16]. Moreover, the stimulation of hormones released by the GI tract promotes adaptation, whereas alternating fasting and feeding periods along with cyclical PN avoid permanent secretion of insulin and fat synthesis.

Enteral – preferentially oral – feeding must be started as soon as possible after surgery. Breastfeeding should be encouraged [17, 18]. Human milk (HM) contains a number of factors supporting the developing neonate's immune system including nucleotides, immunoglobulin A, and leukocytes [19]. HM also contains glutamine and growth factors, such as EGF, which promote bowel adaptation [19]. Polymeric diets are not usually used. However, extensively hydrolyzed formulas are preferred with the advantage of containing short peptides easily absorbed as well as medium-chain triglycerides (MCT) [14]. Amino acid-based formulas (AABF) are generally used in the treatment of food allergies or in case of milk protein hydrolyzate intolerance [20]. True food allergies have been rarely documented in children with SBS. Andorsky reported less intestinal allergy by using AABF, without clearly defining the criteria for the diagnosis of allergy [21]. Two retrospective studies report that the use of an AABF was associated with earlier weaning off PN and also a reduced rate of allergies [22, 23]. However, the very small sample sizes and the lack of control groups in these studies do not support the recommendation of AABF in SBS patients.

Feeds should be increased gradually as tolerated. Tolerance is evaluated by measuring stool number and volume and by the observation of vomiting, irritability, and intestinal distension. Many factors can affect stool volume in SBS, including the length of the residual intestinal segment; the type of segment (the more proximal the

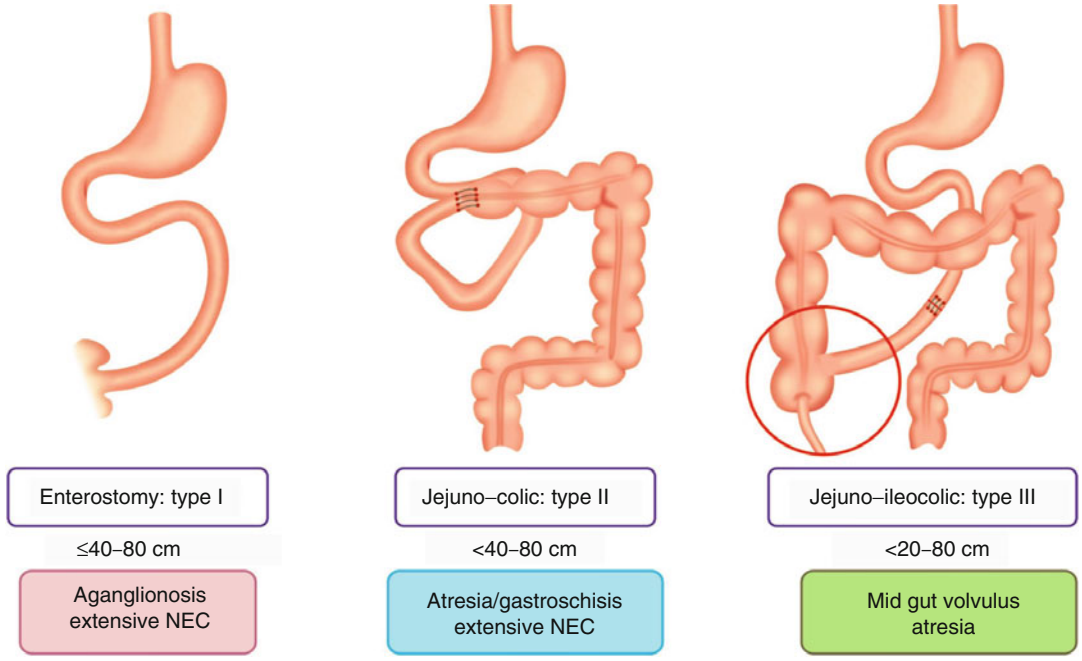


Fig. 1.1 Different types of short bowel syndrome according to the remnant bowel

resection the larger the fluid and sodium losses); the mucosal and endoluminal variables (residual enzymatic activity and absorptive capacity, bacterial overgrowth); the presence of the colon that can absorb large amounts of water, sodium, MCT, and peptides; as well as carbohydrates metabolized to short-chain fatty acid (SCFA) [24]. Continuous aggressive ETF may worsen fluid, mineral, and nutrient malabsorption and may result in severe perianal skin lesions. Bile salt malabsorption should be suspected in children without ICV and/or colon, high stool volume, and perianal injury that can be improved by using cholestyramine. Fluid losses in these patients are often accompanied by sodium and zinc losses and depletion; supplements should therefore be provided [25].

Role of the Colon in SBS

The role of the colon in SBS management and adaptation is crucial by reducing loss of energy and by producing trophic factors [24]. In animal models, supplementation of an elemental diet with pectin, which is fermented to SCFAs in the colon, improved adaptation of the small intestine and colon in SBS [26]. The supplementation of parenteral nutrition with SCFAs or their intracecal infusion reduced mucosal atrophy and intestinal immune dysfunction following massive small bowel resection [27].

In addition to their local effects, systemic SCFAs in animal studies can affect the motility of both the stomach and the ileum through neuroendocrine mechanisms, probably through the expression of proglucagon and peptide YY. Furthermore, both systemic and enteral SCFAs exert a trophic effect on the jejunum by increasing mucosal mass, DNA, and villus height [28]. Since SCFAs are the preferred energy source for colonocytes, in patients with SBS the colon becomes an important organ for calories salvage [29]. Restoration of intestinal continuity, such as anastomosis of the small intestine with the colon, should be done whenever possible. By improving water and

electrolyte absorption, PN can then often be discontinued. In addition anastomosis enables colonic fermentation of unabsorbed carbohydrates from the small intestine to occur, being an important source of energy assimilation. In spite of small intestine malabsorption in patients with SBS, both hyperphagia and adaptation of the remaining colon improve patient outcomes. A study evaluated morphology, proliferation status, and transporters' expression level in the epithelium of the remaining colon of SBS adult patients compared to controls [30]. It seems that in hyperphagic SBS patients with severe malabsorption, adaptive colonic changes include an increased absorptive surface with an unchanged proliferative/apoptotic ratio and well-preserved absorption NHE2, NHE3, and PepT1 transporter mRNA levels [30]. The remnant colon and its associated microbiota play a major role in the outcome of patients with short bowel syndrome (SBS). As mentioned before, preservation of the colon in SBS patients is essential to recovering energy and is consequently a determinant in reducing the need for PN. The essential role of the colon in SBS patients is linked to its own absorptive capability, its adaptive increased absorptive surface, and the metabolic capability of the microbiota. Bacteriological analysis based on culture-dependent methods has found that the microbiota of SBS patients is mainly composed of *Lactobacilli* [31], but neither qualitative nor quantitative information is available regarding the other main bacterial groups. Recent data in pediatric SBS have shown low intestinal microbiota diversity and a dysbiosis [32, 33].

Small Intestinal Bacterial Overgrowth

Cholestatic liver disease (CLD) has been shown to be more frequent in the SBS patients than in any other IF conditions [34]. Out of 175 neonates with abdominal pathology requiring laparotomy (SBS = 40, without SBS = 135), the patients with SBS suffered significantly more morbidity than the group without SBS in all categories of investigation (surgical complications, septic events, CRS, PN weaning delay, liver disease, and duration of hospitalization). The case fatality rate was 37.5 % in patients with SBS versus 13.3 % in patients without SBS ($P = 0.001$). Most of the deaths were caused by liver failure or sepsis and occurred within 1 year from the date of surgery. These patients were for the most part managed by using continuous tube feeding (CTF). It is generally accepted that CTF offers the advantages of optimal digestion and absorption rate [35]. However, continuous infusion changes the intestinal motility pattern by missing fasting period [36]. Significant dysmotility – impairing intestinal bacterial clearance – leads to small intestinal bacterial overgrowth (SIBO) with subsequent Gram-negative sepsis [37–39]. SIBO and cholestasis are common especially in patients without ICV and those having abnormal motility (e.g., intestinal atresia, gastroschisis, NEC). Aggressive continuous ETF is often attempted for mimicking "hyperphagia" with the aim of weaning the child off PN that is thought to be the cause of liver injury. These patients present with dilated loops of bowel containing residual non-absorbed nutrients. This strategy results in increasing SIBO that can cause mucosal inflammation and increased permeability leading to sensitization and allergy as well as bacterial translocation, sepsis, and cholestasis [37–41] (Fig. 1.2). In addition, overaggressive ETF may also result in abdominal discomfort, intestinal distension, and loss of self-regulation of intake leading to eating disorders.

Factors that link infection to cholestasis are either cytokines (mainly TNF, IL-1b, IL-6) or microbial TLR2 or TLR4 agonists [42]. Liver targets primarily include hepatocytes, but also extend to Küpffer cells, cholangiocytes, endothelial cells, and stellate cells. There are no direct studies of bile flow in humans given endotoxin, but there is sufficient indirect evidence to link endotoxin and endotoxin-induced cytokines to cholestasis [43]. During severe sepsis, including septic shock, hyperbilirubinemia is usually a central clinical finding, often out of proportion to typically mild elevations in serum transaminase [44]. Interestingly, TNFa administered in humans has shown

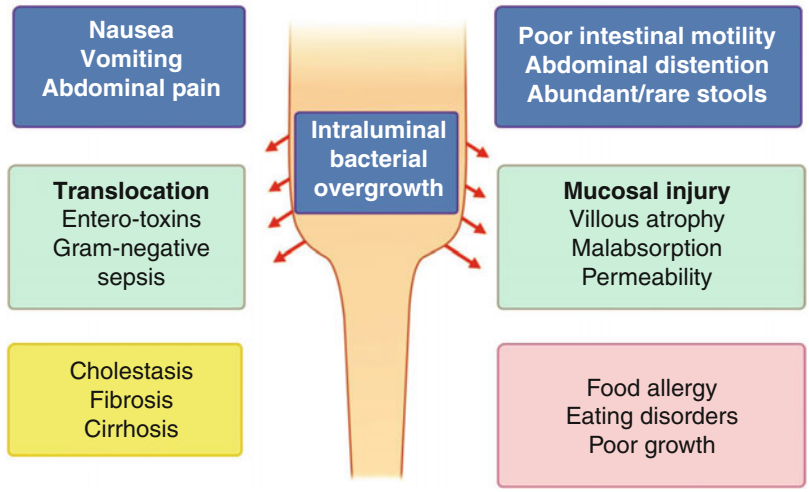


Fig. 1.2 Intestinal and extraintestinal disorders due to complicated short bowel syndrome

significant hyperbilirubinemia, further supporting a link between cytokines and cholestasis [45].

Colonic Hypermetabolism and D-Lactic Acidosis

Clinical manifestations such as abdominal distension, bloating, and nausea – due to colonic microbiological hypermetabolism – may impair daily life and should be monitored. They are the consequences of the intestinal malabsorption leading to a huge load of undigested CHO reaching the colon. This condition may be worsened by hyperphagia or aggressive tube feeding. One rare complication of colonic hypermetabolism, which is different of SIBO, is D-lactic acidosis.

D-Lactic acidosis, also referred to as D-lactate encephalopathy, is a rare neurologic syndrome that occurs in individuals with SBS or following jejunoileal bypass surgery [46, 47]. Fortunately, this complication is very rare. Symptoms typically present after the ingestion of high-carbohydrate feedings. Neurologic symptoms include altered mental status, slurred speech, and ataxia, with patients often appearing drunk. Onset of neurologic symptoms is accompanied by metabolic acidosis and elevation of D-lactate plasma concentration. L-Lactate concentration, which is reflected by serum lactate concentration, is normal. Thiamine deficiency should be excluded [48].

Lactobacilli and other bacteria, including *Clostridium perfringens* and *Streptococcus bovis*, when present ferment unabsorbed carbohydrate to D-lactic acid, which cannot be metabolized by D-lactate dehydrogenase. These organisms may proliferate in an acidic environment that may be promoted by the metabolism of unabsorbed carbohydrates to SCFAs. The mechanism for the neurological symptoms is unknown. They have been attributed to D-lactate, but it is unclear if this is the cause or whether other factors are responsible [49]. Treatments described in case reports have included nothing (with spontaneous resolution), oral metronidazole, neomycin, vancomycin (for 10–14 days), and avoidance of "refined" carbohydrates [50]. Probiotics, prebiotics, and synbiotics have been used but without clear efficacy. Finally, one should consider the intestinal microbiota as a major factor for achieving intestinal adaptation and should be always respected and not be destroyed by unnecessary and/or inappropriate use of oral antibiotics.

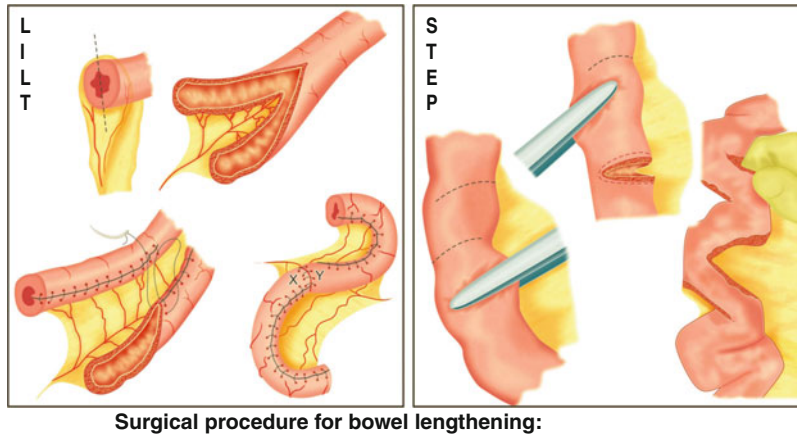
Hormonal Therapy and Other Adaptive Treatments

Hormonal therapy is promising in the management of infants with SBS. Nevertheless, the results of recent trials have largely reduced the enthusiasm around this therapeutic option [51–55]. Recombinant human growth hormone (rhGH) provided inconsistent results with reported side effects in adult trials [51]. A few studies of rhGH alone or in combination with glutamine have been carried out in PN-dependent children with SBS. Despite some decrease in PN requirements during treatment, these trials showed little benefit on body composition and mucosal absorption in the long term [53–55].

Glucagon-like peptide 2 (GLP-2) is produced by the L-cells of the terminal ileum in response to luminal nutrients and has a trophic effect on the intestine, promoting absorption and adaptation [56]. GLP-2 has been shown to increase the surface area of the gut mucosa, upregulate nutrient absorption, improve gut-barrier function, increase intestinal blood flow, and decrease bone resorption. Patients with low levels of GLP-2 following the resection of the terminal ileum and/or the ileocecal valve improved intestinal absorption and nutritional status after treatment with GLP-2 [57, 58]. A recent multicenter study in pediatric SBS provided disappointing results with limited capacity of PN weaning and loss of effects after treatment cessation (ESPEN 2015). Oral insulin has been shown to be beneficial in animal models and might be assessed very soon in infants and children [59, 60]. Other relevant treatments associated with a trophic effect on the bowel mucosa such as short-chain fatty acids may be beneficial in children with SBS [61]. Finally, there is also interest in the use of other trophic factors such as epidermal growth factor (EGF) and insulin-like growth factor-1 (IGF-1) in children with IF and SBS [62].

Non-transplant Surgery for SBS

Several surgical strategies are used to improve the intestinal function in children with SBS having rapid transit time, dilated bowel loops, and insufficient absorptive capacity. Longitudinal intestinal lengthening and tailoring (LILT) and more recently the serial transverse enteroplasty technique (STEP) are the most widely used [63, 64] (Fig. 1.3). Classical conditions and indications for bowel-lengthening surgery include the presence of a large intestinal diameter (>3–4 cm) for at least 20 cm of small bowel and a minimum total bowel length of 40 cm.



Surgical procedure for bowel lengthening:
- **LILT : Longitudinal intestinal lengthening and tapering**
- **STEP: serial transverse enteroplasty**

Fig. 1.3 The longitudinal intestinal lengthening and tailoring (*LILT*) procedure and the serial transverse enteroplasty procedure (*STEP*)

The advantages of the LILT procedure include the conservation of the normal orientation of the muscular fibers allowing more physiological peristaltic contraction, and the possibility to further perform a STEP procedure on the operated segments. The disadvantages are the risk of vascular complications during the operation making LILT more technically demanding as compared to the STEP procedure [65].

The STEP operation involves the use of a surgical stapler applied sequentially from alternating and opposite directions to the dilated loop, in a transverse, partially overlapping fashion creating a zigzag-like channel of approximately 2–2.5 cm in diameter (Fig. 1.3). This operation has the great advantage of being simple and reproducible [65, 66].

These procedures aim not only to enhance the intestinal length but to reduce the diameter of the distended intestinal loop with subsequent reduction of SIBO. A 5-year follow-up cohort study after STEP confirms the efficiency of this procedure. Interestingly, both D-xylose – a marker of carbohydrate absorption and mucosal integrity – and plasma citrulline – a marker of small bowel enterocyte mass – increased significantly postoperatively [67]. This suggests that STEP procedure by reducing SIBO restores small intestinal mucosa integrity and improves villous size within the first weeks following the procedure. Surgical bowel lengthening should be considered in any chronically PN-dependent patient when there is substantial bowel dilatation – regardless of the remaining bowel length [65].

Congenital Enteropathies

Congenital diseases of enterocyte development (CDED) are a group of rare disorders causing intestinal failure in infancy and early childhood. Children with these disorders have early or even neonatal onset of chronic diarrhea that requires PN support [68].

The etiology includes defects in nutrient-electrolyte absorption and disorders of enterocyte differentiation and polarization. Clinically, it is important to differentiate protracted from intractable diarrhea of infancy – the latter being irreversible. Figure 1.4 proposes a simple algorithm to approach newborns and infants with severe diarrhea.

The most common causes of intractable diarrhea of infancy are microvillus inclusion disease

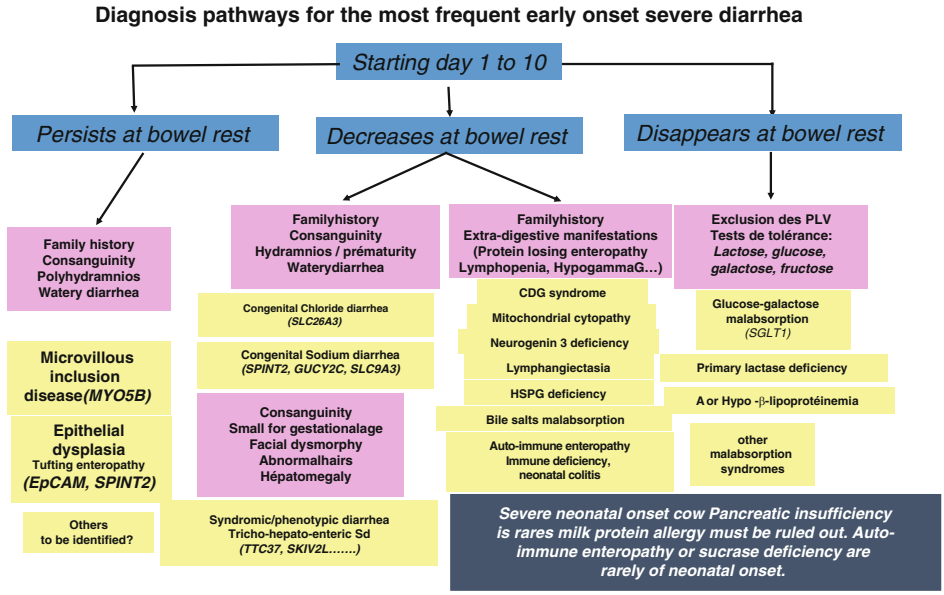


Fig. 1.4 Simple algorithm to approach newborns and infants with severe diarrhea

(MVID, also known as microvillus atrophy), tufting enteropathy (TE, also known as intestinal epithelial dysplasia), syndromic or phenotypic diarrhea, and autoimmune enteropathy. The latter is not considered to be intractable unless all available treatments fail. Several genes responsible for these disorders have been identified by studies based on genome-wide analysis of polymorphisms, adding new tools for the diagnosis of intractable diarrhea of infancy [69].

MVID is due to MYO5B mutation [70, 71]. Severe watery diarrhea develops in the first few days after birth and can rapidly reach a total fecal output of 200–300 ml/kg of body weight per day. Diarrhea does not stop during fasting and causes life-threatening electrolyte and acid-base imbalances, rapid and severe dehydration, and hypovolemic shock. Children with MVID are usually dependent on continuous PN infusion not allowing for cyclic PN. Some patients have associated disorders involving biliary acid metabolism, and some develop liver disease leading to liver failure within the first few years of life [71]. Currently the survival rate for these children is around 70 %, including those patients (up to half) requiring intestinal or liver-intestinal transplantation [72].

Neonates with congenital tufting enteropathy (CTE) develop a severe neonatal diarrhea persisting at bowel rest [73]. Often there is a family history of consanguinity and neonatal deaths related to severe diarrhea and dehydration. Indeed CTE has been found to be associated with mutations in the genes encoding for epithelial cell adhesion molecule (EpCAM and Spint2) [74]. There are reported clusters of cases in the Arabic Gulf area [75]. Infants with CTE typically experience a worsening of diarrhea during continuous ETF even when given extensively hydrolyzed or amino acid-based formula, resulting in failure to thrive and protein-energy malnutrition. Diarrhea is usually less severe than in children with MVID; some patients may be weaned from PN [76]. Nevertheless, most remain PN dependent and sometimes require ITx [73]. Expert histological review of duodenal biopsies is the key to making the diagnosis of this severe cause of IF. The so-called congenital sodium diarrhea (CSD) has been reported as related to SPINT2 mutations [77–79]. Clinical presentation, associated extraintestinal disorders, and histological features suggest a link between CTE and CSD [74].

Syndromic diarrhea (SD), also known as phenotypic diarrhea (PD) or tricho-hepato-enteric syndrome (THE) is a rare congenital bowel disorder [80]. It is characterized by intractable diarrhea starting within the first 6 months of life in most cases and is associated with several other disorders. SD is caused by mutations in TTC37 encoding the uncharacterized tetratricopeptide repeat protein thespin [81] or SKIV2L mutations [82]. This disorder is characterized by life-threatening diarrhea in early infancy, immunodeficiency, liver disease, wooly and poorly pigmented hair, facial dysmorphism including prominent forehead and cheeks and hypertelorism, hypopigmentation, and cardiac defects. Liver disease, including extensive hepatic fibrosis and cirrhosis, affects about half of such patients. There are currently no specific biochemical profiles in these patients although a functional T-cell immune deficiency with defective antibody production has been reported [82]. Microscopic analysis of the hair shows twisted hair (pili torti), aniso- and poikilotrichosis, and trichorrhexis nodosa. Histopathological analysis of small intestine biopsies shows nonspecific villous atrophy with low or no mononuclear cell infiltration of the lamina propria and no specific histological abnormalities involving the epithelium. Early management consists of total PN. Some infants have a milder phenotype requiring partial PN or only enteral feeding. Prognosis of this syndrome is poor but most patients now survive and about half of the patients may be weaned from PN at adolescence. Even treated patients have a short stature and often a mental retardation [83].

Intestinal Motility Disorders

Intestinal motility is under the control of the enteric nervous system that is functionally independent from the central nervous system and is therefore efficient even in completely

disconnected bowel loops, such as intestinal transplants. Normal motility is achieved through the transmission of the signals from the enteric nervous system to the enteric smooth muscle generating healthy peristaltic waves. Therefore motility disorders may derive from either enteric nerve or muscle dysfunction. Although several gastrointestinal conditions are classified among the motility disorders, only a few can lead to intestinal failure: extensive Hirschsprung disease and chronic intestinal pseudo-obstructions (CIPOs).

Hirschsprung Disease

Total or subtotal intestinal aganglionosis (TIA) leaving the child with less than 50 cm normally innervated small intestine below the ligament of Treitz (LOT) is a rare condition [84]. It may be considered as a SBS type 1. Appropriate management strategies are not well established. Surgery is performed as a simple jejunostomy below the LOT with or without or short-segment longitudinal myomectomy. In our practice, nutritional management includes cyclic PN (home PN) associated with oral feeding for reducing the risk of liver disease and promoting oral skills. ITx is undertaken according to the occurrence of complications (water-electrolytes disorders, CRC, and IFALD) and/or the wish of parents for another quality of life. In 12 patients with TIA, we reported an outcome rate of 62.5 % in the LITx group and 75 % in the ITx group, both with half colon grafting [85]. All the surviving patients were fully weaned from total PN, after a median of 57 days. Pull through of the colon allograft was carried out in all patients. Fecal continence is normal in all but one of the surviving children.

Chronic Intestinal Pseudo-obstruction

CIPO is a descriptive term pooling together several disorders of the enteric muscles or nerves. Thus it may have heterogeneous features but has a similar phenotype characterized by recurrent bouts of intestinal obstruction without demonstrable mechanical occlusion. CIPOs are the cause of approximately 15 % of all pediatric cases of IF [1]. Repeated surgical procedures can negatively affect the course of the disease [86].

CIPOs may be due to several diseases that can be either congenital or acquired. The most severe forms are usually congenital and present shortly after birth with episodes of intestinal obstruction. CIPOs have been conventionally divided into two groups, according to the pathogenesis of dysmotility: neuropathies and myopathies. The former is due to the involvement of the enteric nervous system, and the latter is due to the dysfunction of intestinal muscles. CIPOs due to muscle dysfunction are rare but seem to be more severe. Urinary tract disorders such as megacystis and megaureter can be associated both with neuro- and myopathies causing CIPOs. These should be managed by experienced urologists although, surprisingly, they may be better tolerated than other more common obstructive urinary tract disorders [87].

Diagnosis

The diagnosis of CIPOs is based on clinical and radiological analysis. Tools helpful to assess a severe motility disorder include radiological and histological evaluations and, if feasible, gastrointestinal manometry. However, intestinal manometry has never been conclusive for either the diagnosis of CIPO or its treatment. CIPOs management is mainly based on clinical and radiological features. In CIPOs a plain abdominal x-ray typically shows air-fluid levels and dilatation of the bowel loops. Contrast studies, such as the barium small bowel follow-through study, are helpful to rule out mechanical obstruction, but may not reveal motility abnormalities. The presence of a systemic autoimmune disease as well as severe infections and endocrinopathies suggests an acquired form of CIPOs that sometimes can be managed by treating the underlying illness. Congenital forms of CIPOs can be misdiagnosed as Hirschsprung disease, even resulting in surgery. However, surgical biopsies reveal normal enteric ganglia. In these cases bowel resections should be avoided [86]. When CIPO is strongly suspected,

laparoscopic full-thickness biopsies may support the diagnosis with a minimally invasive procedure. Nevertheless, histological hallmarks are scant and the sample should be evaluated in referral centers by expert pathologists who have experience in similar cases and access to specific immunohistochemistry and electron microscopy allowing the recognition of immune-mediated conditions, congenital neuromuscular disorders, and mitochondrial cytopathies [88].

Most patients do not show familial recurrence (sporadic cases), but syndromic autosomal-dominant [89], autosomal-recessive [90], and X-linked [91–94] forms have been described. In particular, an X-linked locus has been mapped to the Xq28 region. Although both familial and sporadic CIPOs have been widely reported, so far only a few genes have been identified as responsible for syndromic CIPO: the thymidine phosphorylase gene (*TP*, also known as endothelial cell growth factor-1, *ECGF1*) [95], DNA polymerase gene (*POLG*) [96], and *SOX10* [97].

Management

Management is based on a multidisciplinary intervention by medical, surgical, and allied professionals. Children with CIPOs almost invariably require some surgical intervention. The major barriers to food progression in patients with inefficient propulsive strength are the natural GI tract bottlenecks: the pylorus and the ileocecal valve. These can cause a functional occlusion of the gastric outlet or small bowel clogging, which can be easily resolved by the formation of a gastrostomy (or jejunostomy) and an ileostomy respectively. The formation of a stoma can improve the quality of life and reduce symptoms in up to 50 % of children with CIPOs [86]. It is sometimes possible to localize the segments of the bowel the most responsible for the dysmotility symptoms: in such cases, a loop resection can improve the intestinal transit and allow enteral feeding and a return to a more normal life [98]. Near total small bowel resection has been proposed as treatment of CIPOs in some cases [99].

Due to the heterogeneity of the syndrome, a key issue is to adapt the treatment/management to each individual patient according to age at onset, severity, and the outcome of surgical procedures such as a primary ileostomy [86]. These children need to maintain the ability and the pleasure to eat normal food, and this can be permitted by taking small and frequent meals with liquids or, in more severe cases, by using the gastrostomy as a venting device; the known benefits of delivering enteral feeding in children with IF make it mandatory to attempt intermittent gastrostomy closure and gastric or gastroduodenal low-fiber feeding [100].

Only a few medications have been shown to improve gastrointestinal motility in patients with an intact enteric nervous system. Erythromycin at low or full antibiotic doses may improve gastric emptying in children with CIPOs and gastroparesis [101]. Several other drugs with a demonstrated effect on gastric motility, such as the serotoninergic agents cisapride and tegaserod, have been withdrawn from the market because of the occurrence of rare but severe cardiac adverse events including arrhythmias, heart attacks, and strokes. Colonic acute pseudo-obstruction can be managed successfully by the infusion of the anticholinergic drug neostigmine, but this drug has not been tested on a long-term regimen [102].

Children with CIPOs may experience small bowel bacterial overgrowth and can thus occasionally benefit from a course of antibiotics such as metronidazole, aminoglycosides, or cotrimoxazole. These drugs should be prescribed only in case of clinical symptoms rather than regularly, in order to avoid the emergence of bacterial resistance.

A French multicenter study including 105 children, 18 with prenatal diagnosis and 80 younger than 12 months of age at onset, showed that early age at presentation, PN dependency and the number of surgical procedures were associated with a poor prognosis [103]. In the most severe forms of CIPOs, children end up with an ileostomy, a gastrostomy with almost permanent aspiration due to gastroparesis, frequent bowel obstructions, and total PN dependency. Patients with such a poor quality of life may benefit from transplantation that should include the stomach (i.e., modified multivisceral transplantation) [104, 105].

Intestinal Failure-Associated Liver Disease

Possible Mechanism of IFALD

IFALD is probably the most relevant and persistent complication affecting children with IF on long-term PN. The prevalence of the disorder is unknown because there is no established definition of liver disease in this setting, and it is unclear as to whether IFALD should be diagnosed on the basis of clinical, biological, or histological criteria. Indeed there are insufficient data on the degree and type of liver involvement in patients with long-term PN [106, 107].

The main factors contributing to liver injury in these patients are recurrent catheter-related sepsis, SIBO with bacterial translocation and release of enterotoxins, and a paucity of oral and enteral nutrition.

Factors affecting the onset and the expression of LD that are specifically related to PN are the inadequate supply of amino acids, the administration of excessive amounts of glucose, the duration of the infusion period, the inappropriate use of lipid emulsions, and, finally, micronutrient imbalances (Table 1.1). It should be stressed that the most important factors leading to IFALD are those related to individual patient characteristics and, importantly, the episodes of sepsis [108–112].

IFALD develops frequently at very early ages, especially in premature infants in whom liver immaturity, frequent sepsis, and necrotizing enterocolitis (NEC) facilitate liver inflammation and severe damages [110, 111]. At this young age, PN is most often administered continuously over 24 h and CRS is common.

An important role in this process is played by liver inflammation caused by extrahepatic infections in which microbial products brought to the liver through the bloodstream, either directly or through production of cytokines, lead to alterations of bile flow. The inflammation associated with these changes may cause rapid fibrosis and eventually biliary cirrhosis with end-stage liver disease [112, 113] (Table 1.2).

Table 1.2 High-risk situations for developing liver disease

Premature and young infants
NEC or gastroschisis ± atresia
Protracted bowel rest/intestinal stasis
Bacterial overgrowth/gram-negative sepsis
Recurrent catheter-related sepsis
Unadapted and/or continuous PN
The combination of the following factors makes cholestatic liver disease likely

Intravenous Lipid Emulsions and Liver Disease and IFALD

Frequently cited observational studies suggested a link between intravenous lipid emulsions (ILE) and liver disease [114, 115]. Ganousse et al. reported that the improvement of cholestasis depends also on maintaining an appropriate protein/energy ratio in PN, achieving cyclic rather than continuous PN infusion, using medium-chain triglycerides-based ILE and adding alpha-tocopherol in ILE [116].

IFALD is a multifactorial disease in which the use of soybean oil-based emulsions (SOBE) in PN may represent the major culprit [117]. Several factors should be taken into consideration when choosing an ILE for parenteral use: the content in essential fatty acids (EFAs), the ratio of ω-6/ω-3, the polyunsaturated fatty acid (PUFA) content, the amount of medium-chain triglycerides (MCTs), and the quantity of alpha-tocopherol and phytosterols.

The probable detrimental effect of ω-6 FAs on liver function is provided by studies that showed that fat emulsions based on pure fish oil (containing ω-3 FAs) have been successful as rescue therapy in pediatric patients with SBS affected by severe liver disease [118]. The infusion of exclusively ω-3 FAs ultimately changed the management of these patients since it allowed the reduction of intake of pro-inflammatory ω-6 and phytosterols while increasing the amounts of alpha-tocopherol, a powerful antioxidant [119].

The evidence gathered on the beneficial effects of fish oil in these patients has led to its use in clinical practice; however, two differ-

ent approaches have been developed in North America compared to Europe. In North America, only a pure fish oil solution (Omegaven®) is available on the market, whereas in Europe it is also possible to use an emulsion containing a mixture of soybean oil (30 %), coconut oil (30 %), olive oil (25 %), and fish oil (15 %) (SMOFlipid®). Both ILEs contain 200 mg/L of alpha-tocopherol.

Some concerns have been raised on providing fish oil as the sole source of lipids over a long period of time. Pure fish oil provides less essential ω-6 fatty acids than that currently recommended in infants and young children [118, 120]. Furthermore, Omegaven® (pure fish oil) can only be given at lower infusion rates compared to SMOFlipid®. Omegaven® may not be able to provide enough calories to sustain growth. Thus, the combination of several types of oil by mixing soybean oil (rich in ω-6 FAs), coconut oil (rich in MCTs), olive oil (rich in MUFAs), and fish oil (rich in ω-3 FAs) appears to promote better growth while limiting hepatic toxicity [120]. Phytosterols contained in soybean oil have been found to be associated with liver disease progression, and their exclusion from intravenous lipid emulsions may also be beneficial in children on PN [121]. Clayton compared the level of phytosterols in plasma of healthy subjects, patients with mild hepatic dysfunction, and those with severe dysfunction who received soybean oil emulsion – rich in sterols – and found a link between liver damage and phytosterol plasma levels [122].

Regarding the presence of tocopherol in lipid emulsions, we should emphasize that there are different preparations of tocopherol: alpha-tocopherol is the form with far greater antioxidant activity. While soybean oil-based emulsions (SOBE) contain a high amount of gamma-tocopherol (which has 25 % of the antioxidant power as compared to alpha-tocopherol), lipids based on fish oil are rich of the most powerful antioxidant vitamin E, alpha-tocopherol [119, 120, 123]. To ensure a proper antioxidant power in lipid preparations, it is advisable to add 0.5 mg of alpha-tocopherol per gram of PUFAs.

A randomized, double-blind, controlled trial on 60 preterm babies stratified by body weight has analyzed a set of parameters (clinical data, laboratory data, fatty acids in plasma and red blood cells, plasma levels of alpha-tocopherol and phospholipids) after infusion of PN with SMOFlipid® or soybean oil-based emulsion [124]. The SMOFlipid® emulsion increased the content of eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids and reduced the ω-6/ω-3 ratio, improving also liver function tests [124].

Another study evaluated the long-term effects of the lipid mixture SMOFlipid® versus a soybean oil-based preparation in pediatric patients on home PN [125]. This randomized, double-blind study involved 28 children who received more than four infusions of PN per week for four consecutive weeks. The infusion was administered in 12–14 h overnight. At the end of the study, no differences between biochemical and nutritional outcomes were recorded, but there was a clear association between the use of SMOFlipid® and a significant decrease of bilirubin levels that conversely increased in the soybean oil-based group [125].

A confirmation of these findings comes from the study of Muhammed et al. who examined the effect of the switch from a soybean oil-based emulsions (SOBE) lipid emulsion to SMOFlipid® in 17 children with cholestasis. The subjects were assigned to a treatment group receiving SMOFlipid® and a group receiving soybean oil-based emulsions (SOBE) lipids. Over a period of 6 months, the use of SMOFlipid® was associated with a marked statistically significant reduction in the levels of bilirubin when compared with the soybean oil-based emulsions (SOBE) lipid group [126].

We can therefore conclude that recent studies have emphasized the superiority of fish oil-derived lipid emulsions as a major advance for the management of patients on long-term PN. Preparations with pure fish oil are effective in improving cholestasis, but their use as the sole source of lipids may not meet essential fatty acid requirements especially in the long term [127]. Nevertheless, while some randomized controlled trials have demonstrated the beneficial effect of SMOFlipid® versus soybean oil-based emul-

sions (SOBE) lipid emulsion, no studies have compared SMOFlipid® to Omegaven® in these patients [124, 125].

Long-Term Management of Intestinal Failure

Home Parenteral Nutrition

Home PN, first used in the early 1980s, allows for full nutritional support of children and adults with temporary or permanent IF at home [128–134]. Survival of children receiving prolonged PN depends mainly on the underlying diagnosis and has increased dramatically during the last three decades; nevertheless, complications such as CRS, IFALD, and loss of venous access can seriously challenge the clinical stability of patients with IF [135–137].

The expertise required to prescribe PN both at home and in the hospital usually comes from a dedicated hospital-based nutritional team who has a thorough knowledge of energy expenditure, nutrients and trace-elements requirements by age, appropriate central catheter handling, and awareness of the risk and complications of long-term PN. Home PN must be tailored to the single patient and its family, always maintaining the goal of counteracting the deleterious aspects of intestinal failure. Official guidelines and position statements on central catheter handling and PN prescription have been published [138].

We followed up 251 children referred to our institution and discharged on HPN between January 1, 2000, and December 31, 2013 (manuscript in preparation). In this survey, 217 children (86 %) had primary digestive diseases. The mean age at HPN onset was 0.7 ± 0.3 year with a mean duration of 1.9 ± 0.4 years. The major indication for HPN was SBS (59 %) secondary to midgut volvulus (16.7 %), necrotizing enterocolitis (12.3 %), gastroschisis (12 %), extensive Hirschsprung disease (10 %), and intestinal atresia (6.4 %). Other PDD were congenital enteropathies (10 %), CIPOS (9.1 %), and inflammatory bowel diseases (IBD, 5.1 %). At the end of the study period, 56 % of children were weaned off home PN, 8 % had intestinal transplantation, and 9.6 % of children died – most of them had immune deficiency. The major complications of home PN were catheter-related bloodstream infections (CRBSI, 1.7 per 1000 days of catheter) and IFALD, 51 children (20 % of the cohort). Children with congenital enteropathies had the highest rates of IFALD (44 % of the subgroup). Children on home PN in our cohort have a shorter HPN duration to weaning, lower death rate, and longer interval to catheter replacement than other studies.

The European data on the long-term management of IF on home PN need to be compared with other continents, especially North America. Several papers from the USA report “intestinal rehabilitation centers” including early management of intestinal failure (IF), especially short bowel syndrome in both neonatology and surgical wards, with the aim of the earliest PN weaning [138–143]. Some patients get severe complications and become candidates for ITx. Some others fail to be weaned off PN and are discharged on home PN when suitable. The organization and follow-up of home PN is supposed to be shared between pediatric gastroenterology-nutrition teams and home caregiver companies according to the local facilities. Unfortunately, there is almost no report in the literature about the prevalence and results of pediatric home PN programs making a comparison with North American management almost impossible. One of the reasons is linked to the organization and the management of IF. In France, patients suffering from IF, especially those with SBS, are managed by specialized medico-surgical departments, including pediatric surgeons and pediatric gastroenterologists-nutritionists or neonatology units. The decision of discharging the child on home PN and the follow-up are fully dependent on pediatric gastroenterology and nutrition teams. The French network is organized regionally. Patients are referred to the closest of the seven reference centers for home PN. Our own history and experience make us the reference center for a large part of the territory. In 2014, the prevalence of home PN for pediatric patients was 262 patients, 108 (41 %) being followed up by our center.

The Importance of a Multidisciplinary Team

Pediatric IF is a multifaceted condition requiring the competent contributions of several medical and allied health professionals both for inpatient and outpatient care. Therefore, the formation of a multidisciplinary team is vital to achieve optimal results [138–145].

The intestinal failure team should ideally include staff specialized in surgery, gastroenterology, and nutrition, a pediatric dietician, and nurses experienced in central venous catheter handling and parenteral nutrition infusion. Special consideration should be given to the link between the hospital team and the home care team. Fostering coordination of surgical, medical, and nutritional management is vital to provide high quality, integrated care of patients with IF, thus improving remarkably the survival of these patients. The three most important issues in the management of children with IF include: (i) a good and early link between primary caregivers and intestinal failure programs, (ii) the presence in the program of both intestinal rehabilitation and intestinal transplantation expertise, and (iii) the participation in the network of the organizations providing home PN solutions. Collaborative strategies must be developed in order to reduce mortality and morbidity in patients with IF, especially for those who are referred for permanent IF or intestinal transplantation [146].

Nutritional Failure and Referral for Intestinal Transplantation

Although a large percentage of children with IF can survive with long-term PN, a proportion of patients eventually develop life-threatening complications such as severe septic episodes, fluid and electrolytes imbalance, loss of venous access for PN, and end-stage liver disease [1, 147]. In these patients, nutrition has failed both in the enteral and the parenteral routes. These patients are said to have "nutritional failure" [1]. They should be referred for intestinal transplantation (ITx).

Nevertheless, relatively few advances have been achieved in the field of ITx and multivisceral transplantation in the last 10 years with no significant improvement in the long-term patient and graft survival. According to the intestinal transplant registry, approximately 2500 ITx have been carried out so far in 79 worldwide transplant centers, of whom half are alive. Among 1351 transplanted children, the 5- and 10-year graft survival rates are reported as approximately 50 % and 30 %, respectively; the 5- and 10-year patient survival rates are similar, approximately 50 % and 30 %, respectively. In patients with a functioning graft, approximately 60 % have a normal function, whereas 40 % require partial PN or intravenous fluids [146]. These sobering figures mandate the adoption of all relevant strategies to avoid ITx until new protocols are available to achieve a better outcome.

There is probably a different threshold for ITx on both sides of the Atlantic Ocean. In accordance with the European approach, we are more reluctant to refer a child for ITx and are inclined to support long-term home PN, which is cost-effective and provides a better quality of life. Support for this view comes from Pironi et al. who have performed a 3-year prospective study including both adults and children on long-term PN for IF [148]. They compared "noncandidates" for ITx (no indications nor contraindications) with "candidates" who had an indication according to the US Medicare and Medicaid Services definitions and a high risk of death or morbidity according to the American Society of Transplantation position paper [149, 150]. The results showed that only patients with nutritional failure due to IFALD or major catheter complications had an increased risk of death on home PN, thus supporting its use as the primary treatment for IF. Therefore it was suggested that ITx should be used only as a life-saving procedure. Although experienced transplantation centers have suggested that the role of ITx should be expanded to a preemptive/rehabilitative procedure applicable to all patients with irreversible IF, the recent findings have shown that home PN is the treatment of choice for IF in adults as well as in children [149, 150]. An early referral is essential to prevent or optimize the long-term management of IFALD. Central venous catheter-related major complications might be indications for a preemptive intestinal transplantation in

selected patients. We therefore believe that only "nutritional failure" should be regarded as a clear indication to ITx.

Isolated liver Tx (LTx) has been performed for IFALD in patients with SBS. Taha et al. reported a group of children with SBS and IFALD who have the potential for adaptation in the residual bowel underwent isolated LTx [151]. The prognosis remains poor after this procedure, eight survivors out of 14 [151]. This procedure should be avoided by preventing liver disease. If performed, it should be exercised with extreme caution. These children need careful assessment before isolated LTx and close follow-up with an experienced multidisciplinary team to monitor nutritional outcomes and may need consideration for transplant or non-transplant surgery in the long term (Fig. 1.5).

In conclusion treatment of permanent IF has made remarkable strides in the past decades. The establishment of multidisciplinary intestinal rehabilitation programs at leading centers has improved the survival of children with IF, while the morbidity associated with both IF and PN has

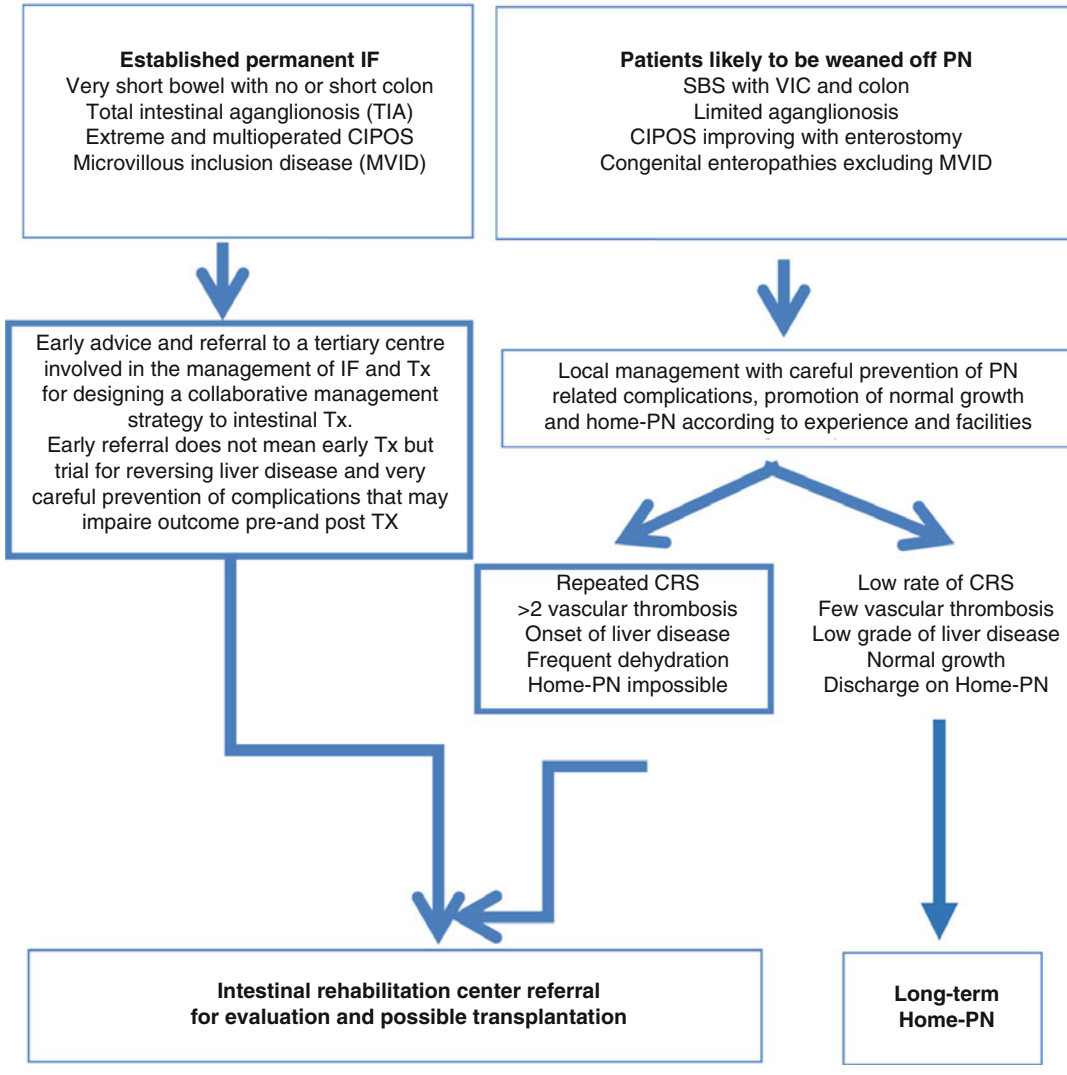


Fig. 1.5 Algorithm for intestinal transplantation

significantly decreased. Recent advances in the knowledge of factors implicated with PN and IF complications and improvements in the medical and surgical management of SBS result in better outcomes for these patients. Isolated liver Tx for SBS patients who have the potential of bowel adaptation should be no longer required. It is interesting to note that the most recent International Intestinal Transplant Registry report at the XIV Small Bowel Transplant Symposium, Buenos Aires, June 2015, showed early evidence of a worldwide trend of 20% reduction in the number of pediatric ITx. This might be explained by at least four factors:

- The provision of guidelines and training [152, 153]
- The development of intestinal rehabilitation centers with increasing IF expertise
- The enlarged use of non-transplant surgery
- The better prevention of IFALD, with fish oil-based lipid emulsions playing a role [127]
- The improved prevention of catheter-related sepsis by using taurolidine or ethanol locks

Major efforts are needed to improve the outcome of ITx that will likely remain part of the armamentarium required to prolong the survival of children with life-threatening complications of IF [152]. Nevertheless, the European experience has led to support a more conservative approach more inclined to home PN, limiting referrals for ITx only to children with nutritional failure.

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Short Bowel Syndrome: Intestinal Adaptation

2

I. Sukhotnik

Abbreviations

SBS	Short bowel syndrome
Caspase	Cysteinyl-aspartate-acid-proteinase
TPN	Total parenteral nutrition
LCFA	Long-chain fatty acids
OKG	Ornithine a-ketoglutarate
GH	Growth hormone
GLP	Glucagon-like peptide
EGF	Epidermal growth factor
TGFβ	Transforming growth factor β
IGF	Insulin-like growth factor
FGF	Fibroblast growth factor
HGF	Hepatocyte growth factor
PDGF	Platelet-derived growth factor

Definition of Short Bowel Syndrome

Short bowel syndrome (SBS) is defined as an intestinal failure following the loss of intestinal length or competence below the minimal amount necessary for the absorption of nutrients and a normal nutritional status [1–3]. The short gut syndrome is a particularly important complication that occurs in newborns and infants suffering from necrotizing enterocolitis, intestinal atresia, and volvulus requiring massive intestinal resection. SBS typically follows resection of 50 % or more of the small intestine and is associated with diarrhea, steatorrhea, dehydration, electrolyte disturbances, malabsorption, and progressive malnutrition [2, 3]. SBS has significant morbidity and is potentially lethal especially when intestinal loss is extensive. An appropriate management of SBS requires reference centers using therapeutic strategies based on a multidisciplinary approach including pediatric gastroenterologists and pediatric surgeons, as well as specialized nurses, dieticians, social workers, and psychologists. This integrated approach should be adapted to each type and stage of intestinal failure including the home parenteral nutrition and transplantation program [4].

A number of mechanisms contribute to malabsorption after massive resection, including acid hypersecretion, hypergastrinemia, rapid intestinal transit (especially likely when the distal ileum is resected or parts of the colon containing peptide YY – the so-called breaking hormone – are lost), impaired residual bowel, loss of surface area, bacterial overgrowth in dilated segments of small bowel, and bile acid depletion. Diarrhea in patient with short bowel syndrome is due to a combination of increased secretions, increased motility, and osmotic stimulation

I. Sukhotnik
Department of Pediatric Surgery and Pathology,
The Ruth and Bruce Rappaport Faculty of Medicine,
Technion-Israel Institute of Technology, Bnai Zion
Medical Center, Haifa, Israel
e-mail: igor-dr@internet-zahav.net

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of water secretion because of malabsorption of luminal contents. Hypertonic concentration of partially digested nutrients in the jejunum results in massive fluid losses that would normally be reabsorbed in the ileum and colon. If the ileum is resected, one of the primary reabsorptive sites for these secretions is lost, and the remaining colon is incapable of reabsorbing most of the fluid. Consequently, patient with distal bowel resection develops usually massive fluid losses in response to large bolus feeding or feedings containing high concentrations of rapidly digested carbohydrates [5]. The degree of malabsorption increases with the length of resection, and the variety of nutrients malabsorbed increases [6, 7]. Balance studies of energy absorption showed that the absorption of fat and carbohydrate was equally reduced to between 50 and 75 % of intake [7]. However, nitrogen absorption was reduced to a lesser extent than that of carbohydrate and fat, namely, to 81 % of intake. Although the ability to absorb many nutrients is decreased following resection, lipid absorption is generally considered the most vulnerable [8–12]. Therefore, patients with short bowel syndrome have been considered to benefit from a low-fat diet early in the course of therapy [13, 14]. Absorption of calcium, magnesium, zinc, and phosphorus is reduced in SBS patient, but does not correlate with the remaining length of bowel [15–17]. Colonic bacteria deconjugate the bile salts entering the colon to free bile acids that stimulate secretion, leading to the development of watery diarrhea. Therefore, the severity of diarrhea following ileal resection depends in part on the length of contiguous colon removed [18]. The gastrointestinal tract is also the site of synthesis of a number of important gastrointestinal hormones and growth factors. Many of these play an important role in regulating gastric emptying and small intestinal transit. Resection of the ileum results in delayed gastric emptying that is a major factor in adaptive increased transit time [19]. On the other hand, resection of the ileum may impair the "colon brake" phenomenon through to be controlled by neurotensin and peptide YY [20]. Other compounds, including prostaglandins, cholecystokinin, and secretin, were not found to adequately maintain the mucosa in the setting of TPN [21]. Gastric acid hypersecretion is a common finding after massive small bowel resection and is proportional to the length of intestine resected. Gastric hypersecretion has been attributed to hypergastrinemia following the loss of gastric peptide production from the resected small intestine [22]. The increased gastric secretions and acidity inactivate pancreatic enzymes, reducing the efficiency of protein and lipid digestion [23]. The excess gastric acid and low intraduodenal pH may damage the bowel mucosa, inactivate digestive enzymes, and stimulate peristalsis [24]. Decreased secretion of cholecystokinin and secretin further reduces gallbladder contraction and pancreatic secretion. These factors along with secretion of a high salt load by the stomach may compound the diarrhea associated with short bowel syndrome [25].

Intestinal Adaptation: Definition

Intestinal adaptation means progressive recovery from intestinal failure throughout which the small bowel increases its absorptive surface area and its functional capacity in an attempt to meet the body's metabolic and growth needs [26]. Although intestinal transplantation has emerged as a feasible alternative in the treatment of children with SBS during the last two decades, intestinal adaptation remains the only chance for survival in a subset of these patients. Intestinal adaptation begins within 24–48 h of resection and includes morphologic (structural adaptation) and functional changes (functional adaptation) of the residual bowel. Structural adaptation includes increasing bowel diameter and length, lengthening the villi, deepening the crypts, and increasing the rate of enterocyte proliferation, finally resulting in increased absorptive surface area and in increased numbers of enterocytes. Functional adaptation entails modifications of the brush border membrane permeability and upregulation of carrier-mediated transport, ultimately resulting in increased nutrient absorption by isolated enterocytes.

In the early twentieth century, it was first observed that the residual intestine can undergo structural changes that result in increased surface area and enhanced nutrient absorptive capacity. In 1957 Piling and Cresson [27] described the first successful extensive resection in two infants, who survived with only 26 and 28 cm of remaining small bowel. Subsequently, many series of patients have documented survival in infants with even shorter small bowel remnants. A review of 50 infants with significant small bowel resection showed a good probability of survival with 15 cm or more of residual gut when ileocecal valve is preserved; a loss of ileocecal valve, however, requires at least 40 cm of residual small bowel for a reasonable chance to survive [28]. Several studies have shown that the functional integrity of the remaining intestine is of far more importance than the outward appearance of the bowel [29]. The nutritional benefits of an increased intestinal absorption in short bowel patients are usually reflected in changes of body weight and composition. The increases in the body weight and lean body and bone mass and the reduction in the fat mass seen as a result of the conservative treatment may be taken as clinical indications of a beneficial effect, which most probably is mediated through the effect on intestinal absorption. In addition, the increase in urine creatinine and the absence of clinical signs of edema supported that the increase in lean body mass, measured by dual-energy x-ray absorptiometry, actually reflects an increase in muscle mass. The increases in serum albumin and sodium are also encouraging [30]. Figure 2.1 illustrates a theoretic graphic presentation of gut function in relation to time after bowel resection.

A "spontaneous adaptation" or recovery of intestinal function is generally described, reaching a plateau at a certain time (usually after 18 months). When trying to improve intestinal adaptation, therapies could either reach a higher plateau phase (given as graph "enhanced adaptation") or reduce the time period until the plateau was reached (given as graph "accelerated adaptation"). Enhanced accelerated adaptation refers to situation when adaptation reaches higher plateau and in shorter time. Accelerating the process may be relevant in patients who are difficult to maintain on parenteral nutrition. However, the maximal increase in the functional absorptive capacity obtained by enhanced adaptation, represented by the level of the plateau, is the aim when trying to wean stable patients from parenteral support.

Intestinal Adaptation: Animal Models

Most studies investigating the process of adaptation have utilized animal models (rat, mouse, and dog) with a jejunoileal anastomosis. Therefore, the relevance of the physiological and structural changes that occur is of unclear clinical relevance to humans who uncommonly have this bowel anatomy remaining. Hyperplasia of the mucosal epithelium, not hypertrophy, is the primary event occurring in intestinal adaptation [30]. In rodent systems, animals subjected to extensive (70 %) intestinal resection undergo a pattern of well-described morphological and functional changes. The remaining intestine changes macroscopically with dilatation, thickening, and an increasing length. There is an increase in villus height and diameter and an elongation of the crypts. Increased villus height and crypt depth is the result of increased proliferation and accelerated migration along the villus and is a marker for the increased absorptive surface area. Increased mucosal proliferation in a functioning intestine, as demonstrated by the increased cell proliferation index following bowel resection, suggests an activated enterocyte turnover and may be considered as a main mechanism of mucosal hyperplasia in residual bowel. An increase in epithelial cellular proliferation, coupled with an increase in apoptosis, produces increases in intestinal RNA, DNA, and protein content [31]. The dynamic process of enterocyte turnover is a function of the rates of crypt cell proliferation, migration along crypt-villus axis, and death via apoptosis. This process may be affected by nutritional status, the route of feeding, and the adequacy of specific nutrients in the diet. Apoptosis or programmed cell death is an active, genetically controlled process of cell

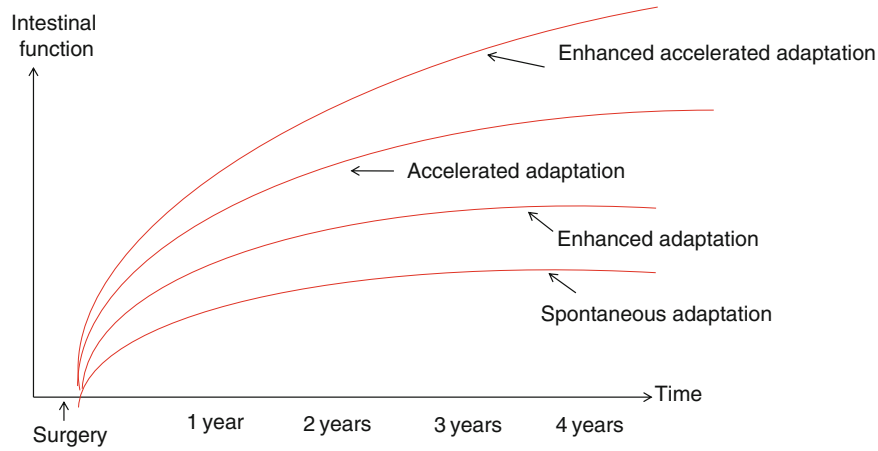

Fig. 2.1 Development of intestinal adaptation as a function of postoperative time

suicide. It is a physiologic process whereby the body disposes of unwanted cells by self-destruction and is our greatest defense against damaged cells [32]. In contrast to necrosis, which is more of an accidental death process, apoptosis comprises highly regulated and reproducible events that eventually lead to cell death. Several regulatory genes affecting apoptosis have been identified and divided into proapoptotic genes (bax, bik, bak, bcl-xs, bad, p53, c-jun, hrk) and antiapoptotic genes (bcl-2, bcl-x_L, rb, mcl-1, a1, brag-1, bfl-1) [33]. Many reports on apoptosis focused on the role of the executioners, cysteinyl-aspartate-acid-proteinases, termed "caspases" which are triggered in response to proapoptotic signals. Caspases cleave numerous substrates at the carboxyl side of an aspirate residue upon induction of apoptosis. A key caspase involved in the apoptotic pathway is caspase-3 (also known as Yama, CPP32, and apopain). Inhibition of caspase-3 has been linked to prevention of apoptotic death in vitro, although certain stimuli can induce apoptosis by a caspase-3-independent pathway [34]. Bcl-2 and related proteins play an important role in the regulation of apoptotic cell death in mammalian systems [35]. At least two family members, Bcl-xs and Bax, act in opposition to Bcl-2. Recent evidence has demonstrated that apoptosis increases in SBS [36]. Enhanced enterocyte apoptosis following bowel resection is considered as being a mechanism that counterbalances the increased enterocyte proliferation in order to reach a new homeostatic status during intestinal adaptation, promoting the disposal of genetically aberrant stem cells and preventing tumorigenesis. In a recent experiment, Jarboe et al. [37] examined the role of *bax* in exaggerated post-resection apoptosis induced by epidermal growth factor receptor inhibition in mice and demonstrated that *bax* is required for the induction of such cell death. Moreover, defective epidermal growth factor receptor signaling augmented resection-induced enterocyte apoptosis via a mechanism that also requires *bax* expression. Functionally there is an increase in absorption per unit length of carbohydrates, proteins, water, and electrolytes [38, 39].

Regulating Intestinal Adaptation

In response to a variety of stimuli, including luminal nutrients, hormones, growth factors, and pancreaticobiliary secretions, the small and large intestine increase their absorptive surface area and functional capacity to meet the body's metabolic and growth needs. Considerable research over many years has focused on the identification of those trophic factors that may promote bowel absorption after massive intestinal resection and provide a successful outcome in patients with SBS. These factors include

nutrients and other luminal constituents, gastrointestinal secretions, hormones, and peptide growth factors [25–27].

Adaptation and Nutrients

The initial management of patients with SBS typically involves TPN. TPN is usually initiated as soon as clinical stability allows and provides adequate total caloric intake and the necessary amounts of nutrients and micronutrients. Importantly, it also "buys time" for gradual tolerance of enteral feedings and successful adaptation of the intestine. However, it is well documented that exposure to intraluminal nutrients is required for stimulation of intestinal adaptation in general and mucosal hyperplasia in particular [40]. Early gradual introduction of enteral feedings also plays an important role in successful postoperative management. It is well documented that exposure to intraluminal nutrients is required for stimulation of intestinal adaptation in general and mucosal hyperplasia in particular [41]. Therefore, many experts in the management of SBS recommend attempting enteral feeding as early as possible. The mechanism whereby food induces this adaptation is unknown. It is likely that enteral nutrition works through a number of mechanisms, including stimulation of mucosal hyperplasia by direct contact with the epithelial cells, stimulation of trophic gastrointestinal hormone secretion, and stimulation of the production of trophic pancreaticobiliary secretions [27, 28]. Although enteral feeding is one of the major trophic factors in the stimulation of intestinal adaptation, not all nutrients have equal stimulating trophic effects. Growing evidence suggests that glutamine, pectin, short-chain fatty acids, and long-chain fatty acids are considered the most effective among the factors promoting post-resection intestinal adaptation [41]. Although lipid absorption is generally considered the most vulnerable in SBS patient, growing evidence suggests that long-chain fatty acids appear to be more effective stimulators of intestinal adaptation than either medium-chain fats or carbohydrates [42]. Early exposure to a high-fat diet augmented and accelerated intestinal regrowth after massive small bowel resection in a rat model [43]. In addition, dietary lipids increased the absorptive capacity of the intestinal remnant, improved food and fat absorption, and restored plasma and tissue lipid content in this model [44]. In contrast, a low-fat diet significantly affected adaptive responses by an inhibition of enterocyte proliferation and did so independently of enterocyte apoptosis [45]. Depletion of dietary fat inhibited also cellular and molecular mechanisms of LCFA absorption by isolated enterocytes in the same model. This was evident from a decrease in LCFA plasma-membrane transport protein fatty-acid translocase (FAT) (the rat homologue of human CD36) and a decrease in isolated enterocyte [3H]-oleate uptake as measured by established cellular LCFA transport assay [46].

Extensive studies in various experimental models of SBS have established that many amino acids (e.g., glutamine) strongly stimulate the intestinal adaptive response. Glutamine, rather than glucose, is the major fuel for mitochondrial respiration in enterocytes. Glutamine is used for protein synthesis either directly or as a result of catabolic pathways. Within 24 h of 80 % small bowel resection in the rodent, glutamine and total amino acid uptake per gram of tissue is increased [47]. However, with the decrease mass of tissue, overall glutamine consumption in the long term is less than controls, and muscle stores of glutamine remain unchanged [48, 49]. The addition of glutamine or arginine to enteral feeds after extensive resection does not seem to produce a consistent effect between studies; indeed, there is little evidence that either amino acid increases adaptation, with some groups reporting lower protein and DNA levels than controls [50]. Supplementation of enteral feeds with ornithine a-ketoglutarate (OKG), the soluble ornithine salt, does seem to have a positive effect on intestinal adaptation and mucosal polyamine synthesis [51]. However, another nonessential amino acid arginine impairs post-resection intestinal regrowth in rats through a decrease in enterocyte proliferation and increase in cell death via apoptosis [52].

Vitamin A is essential for normal growth and for differentiation of epithelial tissues. Extensive studies in various experimental models have established that vitamin A may regulate intestinal epithelial cell proliferation and regeneration. Swartz-Basile et al. [53] examined the mechanisms by which the status of vitamin A affects adaptation by analyzing proliferation, apoptosis, and enterocyte migration in the early postoperative period after bowel resection in rat. Both crypt cell proliferation and enterocyte migration rates were significantly decreased in the vitamin A-deficient rats subjected to submassive small bowel resection. In contrast, apoptosis was significantly greater in the remnant ileum of resected vitamin A-deficient rats compared to control animals. The authors concluded that vitamin A deficiency inhibits intestinal adaptation following partial small bowel resection by reducing crypt cell proliferation, by enhancing early crypt cell apoptosis, and by markedly reducing enterocyte migration rates.

Intestinal Adaptation and Hormones

It is widely accepted that the adaptive response is controlled in part by the release of one or more of the gut signaling hormones. These include enteroglucagon, neurotensin, peptide YY, growth hormone, and insulin-like growth factor [20]. Additionally, enteral feeding stimulates the release of enterotrophic hormones (gastrin, cholecystokinin, neurotensin) which have an important role in the process of gut adaptation. There is growing evidence in animal models of SBS that some hormonal manipulation can improve intestinal adaptation.

Growth hormone (GH) is a single-chain protein produced in the anterior pituitary gland. Because GH has been shown to induce growth and proliferation in many different tissues and cell lines and the receptor for growth hormone has been found throughout the intestine, its role in the setting of SBS has been studied extensively. Many studies in various experimental models of SBS have established that exogenous administration of growth hormone enhances mucosal hyperplasia and increases water, electrolytes, and nutrient absorption [54, 55]. In a rabbit model of SBS, Avissar et al. [56] recently demonstrated that treatment with growth hormone for 2 weeks restored a Na(+)-dependent broad-spectrum neutral amino acid transporter (ATB(0)/ASCT2) protein in the jejunum and ileum, which is responsible for downregulated glutamine transport in rabbit residual bowel following 70 % small bowel resection. Many studies in various experimental models of SBS have established that exogenous administration of growth hormone enhances mucosal hyperplasia and increases water, electrolytes, and nutrient absorption [54, 55]. Treated animals have shown mucosal hyperplasia and increased absorptive capacity above and beyond the normal adaptive response after small bowel resection. Other studies have demonstrated increased villus height and crypt depth, positive nitrogen balance, and bowel growth when rats were given GH combined with glutamine and/or a diet high in protein [57, 58]. These studies do not discredit GH as a driver of adaptation but underscore the interplay between the many factors involved in adaptation in SBS. Another very promising observation is that GH may augment the length of the remnant intestine after bowel resection. This finding is particularly important when you consider that remnant intestinal length is the greatest predictor for long-term parenteral nutrition requirement.

Since Wilmore et al.'s [59] demonstration that a combination of growth hormone, glutamine, and a specialized diet enhances intestinal compensation and optimizes nutrient absorption in patients with intestinal failure, many similar studies were conducted and yielded inconsistent results. For example, Matarese et al. performed a systematic search on electronic databases and the Internet for the purpose of compiling the evidence published to date on this subject. The authors concluded that the administration of recombinant human growth hormone alone or together with glutamine with or without a modified diet may be beneficial when the appropriate patients are selected for treatment [60].

Enteroendocrine glucagon-like peptides GLP-1 and GLP-2 are synthesized and released

from enteroendocrine cells in the distal small intestine and large intestine. GLP-1 promotes efficient nutrient assimilation, while GLP-2 regulates energy absorption via effects on nutrient intake, gastric acid secretion and gastric emptying, nutrient absorption, and mucosal permeability [61]. Evidence that GLP-2 is important in controlling intestinal adaptation following bowel resection has come from experiments by Litvak et al. [62]. In addition, Martin et al. [63] have recently shown that luminal nutrients stimulate bowel growth and differentiation by stimulation of GLP-2 secretion and that GLP-2 levels significantly correlated with the magnitude of intestinal resection and nutrient malabsorption. Uluutku et al. [64] investigated the trophic and functional effects of bombesin on the remaining gut in rats with SBS and showed an increased absorptive capacity and improved serum protein and albumin levels following bombesin administration, even in the absence of elemental nutrition. In another recent study, treatment with bombesin resulted in a significant increase in accelerated cell turnover after massive small bowel resection in a rat [65]. The obese gene protein product leptin is a hormone that is secreted from adipocytes and acts primarily on the hypothalamus regulating energy expenditure and food intake [66–68]. Recent study has shown that treatment with leptin enhances structural intestinal adaptation, increases enterocyte proliferation, and decreases cell death via apoptosis following massive small bowel resection in a rat [69].

Because of its antisecretory properties, somatostatin has been advocated for the treatment of patients with SBS. Somatostatin decreases diarrhea and stoma output following massive small bowel resection. However, recent experimental evidence suggests that Sandostatin decreases cell proliferation and inhibits structural intestinal adaptation following massive small bowel resection in a rat model [70]. In light of these results, somatostatin should be avoided following massive small bowel resection in order to prevent its inhibitory effects of bowel regrowth.

Little is known about the effects of gender and sex hormones in short bowel syndrome. A growing body of literature points to gender differences in many diseases as well as gender dimorphism in the response to trauma, shock, and sepsis. Current theories for the different responses to these events between genders are based on gonadal, hypothalamic, and pituitary hormone levels. In a recent study, the effects of gender and sex hormones on structural intestinal adaptation were investigated following massive small bowel resection in a rat [71]. This study confirms that bowel regrowth following massive small bowel resection is not gender related. Depletion of androgen by castration inhibited intestinal adaptation, and testosterone showed a strong stimulating effect on bowel regrowth.

Adaptation and Peptide Growth Factors

Over the past decades, several proteins produced by different cells and tissues, designated peptide growth factors, have been reported to play an important role in stimulating enterocyte turnover. Our understanding of the structure and function of the peptide growth factors has advanced rapidly in recent years. Peptide growth factors appear to mediate many of the processes required for normal intestinal growth and differentiation. Every growth factor modulates growth through autocrine, juxtacrine, or paracrine mechanisms and usually acts as a mitogen through the stimulation of specific cell surface receptors. It has been reported that growth factors stimulate cell proliferation through the alteration of transcription of various genes [72]. Peptide growth factors are often divided into several groups based on their structure and mode of induction and include the epidermal growth factor (EGF) family, the transforming growth factor-β (TGF-β) family, the insulin-like growth factor (IGF) family, and the fibroblast growth factor (FGF) family. In addition, a smaller number of peptide growth factors having different structural properties compared to the main families also have been identified within the gastrointestinal tract. These include hepatocyte growth factor (HGF), platelet-derived growth factor (PDGF), trefoil peptides, hematopoietic stem cell factors, and many more [73].

Certain peptide growth factors have been evaluated for their role in modifying cell proliferation and in stimulating the enterocyte functional activities in animal models of short bowel syndrome. The effect of other factors has not been evaluated following bowel resection, and further work is required to study its effect on intestinal adaptation. EGF was initially isolated by Cohen in 1962 from mouse submandibular salivary glands as the factor responsible for promoting premature eyelid opening in neonatal mice. EGF is a multifunctional, 53-amino-acid peptide that acts through stimulation of specific cell surface receptors. EGF exerts a variety of biological influences in numerous cell populations. Among these, EGF was shown to regulate proliferation of gastrointestinal epithelium through interaction with the enterocytes at the luminal surface as well as increases functional capacity of the gastrointestinal tract mucosa. EGF has been shown to augment the intestinal adaptation in animal models of SBS. Multiple studies have suggested a positive effect of EGF on both structural [74] and functional [75] parameters of intestinal adaptation. The second member of the EGF family, transforming growth factor-α (TGFα), is a 50-amino-acid polypeptide which was first identified in nontransformed fibroblast indicator cells in soft agar and was found to promote anchorage-independent growth of these cells [76]. TGFα shares many structural homologies to EGF and appears to act through the same receptor as EGF. Since its isolation from transformed cell lines, TGFα has been demonstrated to directly promote cell proliferation and to exert a trophic effect on intact gastric, intestinal, and colonic mucosa. Recently, the effect of TGFα on intestinal adaptation has been evaluated in a mice model of SBS. Falcone et al. [76] have reported that in mice with SBS, intestinal adaptation occurs despite the absence of TGFα expression in the remaining bowel; however, exogenous TGFα stimulated enterocyte proliferation and intestinal adaptation. The insulin-like growth factor family includes three peptides: insulin, insulin-like growth factor I (IGF-I), and insulin-like growth factor II (IGF-II). The positive effect of IGF-I and IGF-II in stimulating bowel regrowth after intestinal resection has been reported by many investigators [77, 78]. In a recent study, oral insulin supplementation dramatically enhanced structural intestinal adaptation after massive bowel resection in a rat [79]. This effect was much more significant than the one observed previously following parenteral insulin administration and was correlated with insulin receptor expression along the villus-crypt axis [80]. Based on these studies, a pilot study was performed to examine whether oral insulin supplementation decreases the need for parenteral nutrition in pediatric patients with SBS. In this trial, clinical improvement was observed in a subset of children, and two of ten infants were successfully weaned off parenteral nutrition [81]. In the intestinal mucosa, numerous cytokines were shown to affect epithelial cell differentiation and proliferation through epithelial-mesenchymal and epithelial-immune cell interaction. Transforming growth factor-beta family includes TGF-β1 and several peptides exhibiting various degrees of homology to this prototypic member. TGF-β1 was first isolated from human platelet as a large propeptide of 391 amino acids with the characteristics of secretory polypeptide. TGF-beta has been found to inhibit proliferation of all epithelial cell proliferation of all epithelial cell populations through prolongation of the G1 phase. Therefore, probably, there are no works studying the effect of TGF-β on intestinal adaptation following massive small bowel resection. The most interesting possibility, but one that is speculative at present, is that TGF-beta in conjunction with TGF-alpha can contribute to the regulation of the dynamic turnover of the intestinal epithelium in adapting gut. Additionally, TGF-beta may affect bowel growth through its stimulating effect on extracellular matrix. Fibroblast growth factors play key roles in controlling tissue growth, morphogenesis, and repair in animals. Recent study has shown that keratinocyte growth factor (fibroblast growth factor VII) plays a positive role in intestinal regrowth in a mouse model of SBS [82]. The effects of other fibroblast growth factor family members, transforming growth factor-β family, and platelet-derived growth factor on bowel growth have been examined in normal intestine, but have not been

evaluated in an animal model of short bowel syndrome. Future experiments will, therefore, be needed to examine the role of these factors and to elucidate the potential mechanisms by which they affect the adaptive response. Hepatocyte growth factor (HGF) is a distinctive growth-modulating peptide, which has been identified in primary hepatocytes and is also expressed in the stomach, small intestine, and colon. HGF was found early in all human fetal digestive tissues, suggesting its morphogenic role in digestive system development during embryogenesis [83]. It has been reported that intestinal mesenchyme secretes HGF which stimulates the growth of attaching epithelial cells by a paracrine mechanism [84]. Comparing the effect of TGF-alpha, TGF-beta, keratinocyte growth factor, and hepatocyte growth factor on restitution of intestinal epithelial cells, Nishimura and collaborators have shown that HGF was the most potent of the cytokines in accelerating repair of the damaged monolayer of the intestinal epithelium [85]. Further experiments demonstrated that HGF can increase intestinal epithelial cell mass and function in vivo. After reviewing the evidence for the role of HGF as a pro-adapting agent after bowel resection, it should be mentioned that recent work by Schwartz and colleagues [86] has demonstrated dramatic response in mucosal mass and enterocyte functional capacities following bowel resection in rats exposed to HGF.

Enhancing Adaptation in the Treatment of Short Bowel Syndrome

Early management of SBS in reference centers by multidisciplinary groups is certainly the key issue to recognize, as early as possible, irreversible intestinal failure, to improve its outcome, and to perform intestinal transplantation in an appropriate time. Management of SBS has traditionally been divided into three phases: an acute phase, an adaptation phase, and a maintenance phase. Phase I, the acute phase, occurs during the immediate postoperative weeks and may last 1–3 months. This phase is marked by poor absorption of almost all nutrients, including water, electrolytes, proteins, carbohydrates, fats, vitamins, and trace elements [87]. Fluid loss from the gastrointestinal tract tends to be greatest during the first few days after massive small intestinal resection; ostomy outputs may exceed 5 L/day. Aggressive fluid and electrolyte replacement therapy is necessary to reduce life-threatening dehydration, hypotension, and electrolyte imbalances. Frequent measurements of vital signs, intake and output, and central venous pressures are required because of rapid metabolic changes and possible hemodynamic instability [88]. Phase II, the adaptation phase, generally begins within 24–48 h after resection and may last from 1 to 2 years. During this period, 90–95 % of the bowel adaptation potential (including nutritional and metabolic stability) has been realized, and only 5–10 % of additional improvement in bowel adaptation and absorption is possible [89]. Adaptive changes also take place in the stomach, pancreas, and colon. Clinical manifestations of intestinal adaptation include weight change and stabilization of fluid and electrolyte levels [87]. By phase III, the maintenance phase, the absorptive capacity of the gut is at a maximum. Although some patients still require parenteral nutrition, others do well on diet alone. Attempts should be made to compensate for continued malabsorption by increasing the quantity of small meals and supplementation with vitamins and minerals [90]. At this point, the patient has either adapted maximally so that nutritional and metabolic homeostasis can be achieved entirely by oral feeding, or the patient is committed to receiving supplemental or complete nutritional support for life, either by ambulatory home TPN or specialized enteral or oral feedings.

An increasing number of factors have been identified that can promote epithelial growth, increase epithelial absorptive function, and affect intestinal growth. Recent clinical trials offer the potential of a new modality to care for such patients. Selection of appropriate patients for these new therapies and ensuring efficacy of these factors will be important objectives over the next several years [91, 92]. In a pilot study, enteral treatment with epidermal growth factor in pediatric SBS improves

nutrient absorption, increases tolerance with enteral feeds, and improves the infection rate [93]. Two clinical studies in adult SBS patients show extremely encouraging results of glucagon-like peptide 2 (GLP-2). In a non-masked study of eight SBS patients, a number of positive effects of GLP-2 were noted [94]. These patients lacked a distal small bowel and colon and thus had very little endogenous GLP-2 and were without the normal postprandial elevation in GLP-2 levels. Nutrient absorption was carefully measured in this study and was found to increase by 3.5%. A significant increase in protein absorption, and a nonsignificant increase in carbohydrate absorption, was noted; however, no significant change was found in fat absorption.

Morphometric analysis of the small intestine demonstrated an increase in villus height and crypt depth in the majority of their patients. Teduglutide is a protease-resistant analog of GLP-2 for the potential treatment of gastrointestinal disease. Teduglutide has prolonged biological activity compared with native GLP-2, and preclinical studies demonstrated significant intestinotrophic activity in models of SBS, experimental colitis, and chemotherapy-induced intestinal mucositis. Patients with SBS rely on parenteral nutrition following bowel resection, and in a phase III clinical trial with teduglutide, >20% reduction in PN was observed in patients with SBS receiving teduglutide [95].

In a recent pilot study, oral insulin supplementation decreases the need for parenteral nutrition in pediatric patients with SBS with clinical improvement in a subset of children, and two of ten infants were successfully weaned off parenteral nutrition [81].

Stem Cells and Intestinal Adaptation

Intestinal stem cells (ISCs) are fundamental cornerstones in intestinal biology, ensuring homeostatic self-renewal of intestinal mucosa and presenting a reserve pool of cells that can be activated after tissue injury (ischemia-reperfusion) or after bowel resection. Intestinal stem cells are characterized by their ability to self-renew as well as to differentiate into specialized cells, properties critical for tissue maintenance and regeneration. ISC compartment has long been known to reside near the crypt bottom; however, the definitive identification of ISCs has been hampered by a lack of unique molecular markers (Fig. 2.2).

Two hypotheses exist regarding the exact identity of the ISCs: the +4 position model and the SC zone model. Both concepts are based on the assumption that every crypt contains approximately 4–6 independent ISCs. According to the +4 position hypothesis, the ISCs reside at position 4 relative to the crypt bottom, while the first three positions are occupied by the terminally differentiated Paneth cells. Potten and colleagues reported that these +4 cells retain DNA labels throughout long periods of time [96] and are extremely radiation sensitive [97]. The second (SC zone) hypothesis was put forward after the identification of a unique small cycling cells interwedged between the Paneth cells (so-called crypt base columnar (CBC) cells). Bjerknes and Cheng proposed that these CBC cells represent the true intestinal SCs [98].

+4 stem cells (which occupy the fourth position from the crypt base) reside at position 4 relative to the crypt bottom, while the first three positions are occupied by the terminally differentiated Paneth cells. Multipotent LGR5+ (Leu-rich repeat-containing G protein-coupled receptor 5-expressing) crypt base columnar stem cells drive regular epithelial renewal.

Until recently, there had not been consistently reliable markers to identify these intestinal stem cells. However, several intestinal stem cell markers including *Musashi1*, *Lgr5* (leucine-rich repeat-containing G protein-coupled receptor 5), and *DCAMKL-1* (doublecortin and CaM kinase-like-1) have been identified. *Musashi1*, an RNA-binding protein, was originally thought to be a neural stem cell marker. However, subsequent studies demonstrated that *Musashi1* was also present on intestinal and colonic stem cells [99]. Utilizing this marker, the isolation of an unpure culture of intestinal stem cells from the jejunum was achieved.

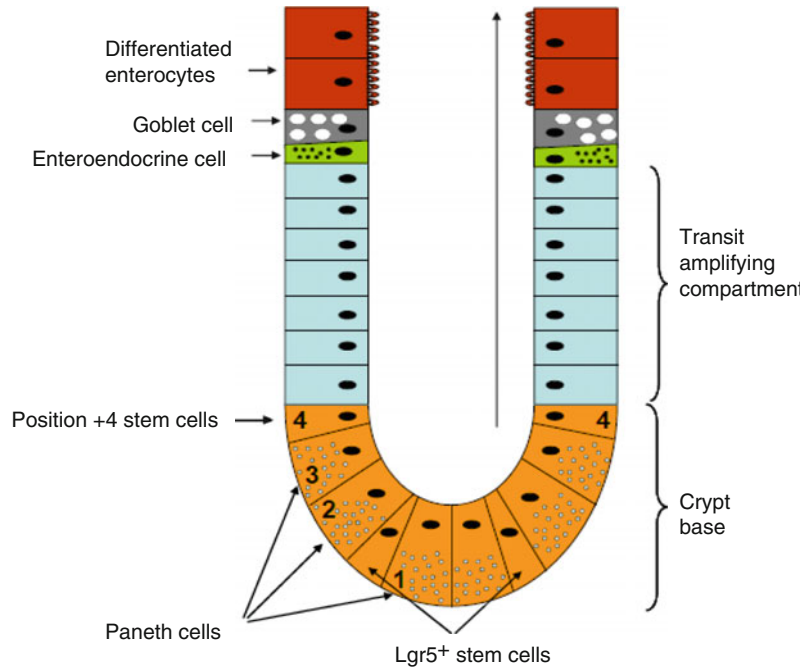

Fig. 2.2 Model of epithelial regeneration in the small intestine

However, additional markers were clearly needed to purify this culture. Wnt signaling has been implicated in different stages of mammary development as well as in mammary oncogenesis [100]. *Lgr5* has recently been discovered and has been shown to exist exclusively in crypt base cells within the intestine. Studies examining intestinal stem cell signaling have also suggested that *Wnt*/*Ephrin*, *BMP* (bone morphogenic protein), *Notch*, and *PI3K*/*PTEN* (P-phosphatase and tensin homologue) signaling cascades are dramatically involved with intestinal stem cell proliferation and lineage commitment.

Experiments designed to further purify intestinal stem cells are certainly required prior to their widespread use. Once the mechanisms of stem cell proliferation are elucidated, intestinal stem cells may be deemed the most optimal stem cell to seed tissue-engineered grafts or to apply to injured tissues during therapy.

Stem cells represent a novel treatment modality with increasing therapeutic potential. The extensive proliferation and differentiation capacities of stem cells make them optimal for seeding tissue-engineered grafts. Stem cell-engineered bioprosthetic neointestine may prove beneficial in conjunction with these techniques to increase the absorptive capacity of the intestine in short bowel syndrome. In this regard, supplying an adequate number of functional stem cells to affected patients, either through tissue-engineered neointestine or via stem cell transplantation, may increase overall enteric function, promote intestinal restitution, and relieve disease symptoms. Such procedures have already shown benefit in animal models and may decrease the need for long-term parenteral nutrition or multivisceral organ transplantation [101]. In addition, the release of protective factors (paracrine effects) has also been shown to be beneficial to growing intestine.

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Bacterial Overgrowth and Intestinal Microbiome

3

Jason Soden

Abbreviations

CFU	Colony-forming units
MMC	Migratory motor complex
SIBO	Small intestinal bacterial overgrowth
SBS	Short bowel syndrome
HBT	Hydrogen breath test
NEC	Necrotizing enterocolitis

Background, Microbiology, and Etiology

Intestinal failure is the end result of various etiologies that may affect gastrointestinal function to the extent that parenteral nutrition is required to maintain adequate fluid, electrolyte, or energy balance. The causes of intestinal failure may be due to an insult in anatomy, motility, or mucosal function. Although the individual disorders that lead to intestinal failure are diverse, there are common themes in gut dysfunction that influence natural history, prognosis, and therapeutic targets. One such area is the intestinal microbiome and its central role in the pathogenesis of intestinal failure and its inherent complications.

The microbiome, a dynamic ecosystem of intraluminal microorganisms, can be thought of as the playing field where the various aspects of intestinal health and disease compete. Gut bacteria both influence and are influenced by the host's nutritional intake, gastrointestinal anatomy and motility, mucosal inflammatory pathways, and extraintestinal organ systems. The microbiome has been well studied in a myriad of human diseases, including inflammatory bowel diseases, functional gastrointestinal disorders, liver disease, obesity, cardiovascular disease, and more [1, 2]. The symbiotic relationship between the host and the intestinal microbiome defines various physiologic processes that result in a mutually beneficial interaction between the two. A classic example of symbiosis in human intestinal failure is the carbohydrate salvage pathway, whereby colonic bacteria ferment malabsorbed dietary carbohydrates, yielding short-chain fatty acids that can be utilized as an energy source by colonocytes. The fatty acids further act to acidify the colonic milieu, which inhibits the growth of pathogenic gram-negative aerobic bacteria [3]. The intestinal microbiome functions as a diverse population of bacteria, with a delicate and balanced interaction between colonies of organisms. Dysbiosis, a pathologic state derived from imbalance in the microflora population, may be a key component to downstream complications in

J. Soden, MD
Pediatric Gastroenterology, Hepatology, and Nutrition, University of Colorado School of Medicine, Children's Hospital Colorado, Aurora, CO, USA
e-mail: Jason.Soden@childrenscolorado.org

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intestinal failure. Perhaps more notorious in intestinal failure is the concept of small intestinal bacterial overgrowth (SIBO), whereas colonic flora overpopulate in the small intestine leading to clinical symptoms.

The intestinal lumen houses an immense number and diversity of microbial species. In a healthy state, the proximal small intestine contains 10^3–10^5 colony-forming units (CFU) bacteria per milliliter (mL) fluid. This number increases to an estimated 10^{10}–10^{12} CFU per mL in the colon. Small intestinal bacterial overgrowth is therefore defined as $>10^5$ CFU bacteria per mL duodenal or jejunal fluid. Although this quantitative estimate is important, patients may manifest clinical symptoms with bacterial counts that are less than this presumed cutoff. Similarly, patients may remain clinically asymptomatic with a larger small intestinal bacterial burden. Therefore, aside from the number of bacterial CFU, the types of bacteria play a crucial role as well. The human gut contains >500 microbiological species. These bacteria have a characteristic distribution from mouth to anus (Fig. 3.1). In the setting of small intestinal bacterial overgrowth, the small intestine is overpopulated by colonic-type flora, namely, gram-negative coliforms, gram-positive anaerobes, and enterococci. This entity is common in intestinal failure. Gutierrez and Duggan reported their results of duodenal aspirates from pediatric patients with intestinal failure, in which 70 % of patients had bacterial overgrowth (defined as duodenal aspirate $>10^5$ CFU/mL), with predominant species including *S. viridans*, *Enterococcus*, *E. coli*, and *Klebsiella* [4].

In a healthy state, intestinal bacteria play a role in several key physiologic functions. Luminal bacteria are involved in nutrient metabolism, including degradation and absorption of amino acids, starches and complex carbohydrates, and fat, in addition to micronutrient and vitamin metabolism (vitamin K, vitamin B12, and folate). Bacterial conjugation of intraluminal bile acids is integral to micelle formation and dietary fat absorption. The carbohydrate salvage pathway supports short-chain fatty acid production, which influences cell proliferation, intestinal adaptation, and energy recovery [5]. The interaction between bacteria and the gut epithelium is critical to the maintenance of mucosal integrity. From an immunologic standpoint, the interplay between bacteria and the host immune system influences immune conditioning, tolerance, and homeostasis. All of these functions are likely to be influenced by a balanced intestinal microbiome, which further maintains proper nutrient competition and bacterial population homeostasis.

Furthermore, the physiologic state of the microbiome is maintained by several intestinal functions. Luminal pH gradient, which is regulated by gastric, pancreatic, and intestinal secretions, influences bacterial population and anatomic distribution of colonies. Pancreatic secretions have additional bacteriocidal properties, and therefore dysbiosis and overgrowth are found in chronic pancreatitis [6]. The gut mucosa contains an elaborate network of immunologic cells, mucous layer, and nutrient byproducts which stimulate and fuel bacterial subpopulations and maintain homeostasis. From an anatomic standpoint, the ileocecal valve is an established barrier that prevents retrograde contamination of colonic flora into the small intestine. Finally, the enteric nervous system fires regular contractions through the MMC Phase III contractions that play a critical housekeeping role.

In the patient with intestinal failure, several perturbations in these physiologic processes may lead to alterations in gut microbial homeostasis (Table 3.1). Perhaps the most widely recognized category involves alterations in the host anatomy that predispose to bacterial overgrowth. In short bowel syndrome, which accounts for the majority of both pediatric and adult intestinal failure [7], the foreshortened intestine has altered function typically following surgical resection. The neonatal patient with congenital intestinal atresia or gastroschisis typically has dilated small intestine that may be dysfunctional, leading to altered motility and stasis. Anastomotic narrowing and strictures may create stagnant proximal loops of bowel that fester luminal overgrowth. It is well established that the absence of the ileocecal valve propagates retrograde contamination of the small

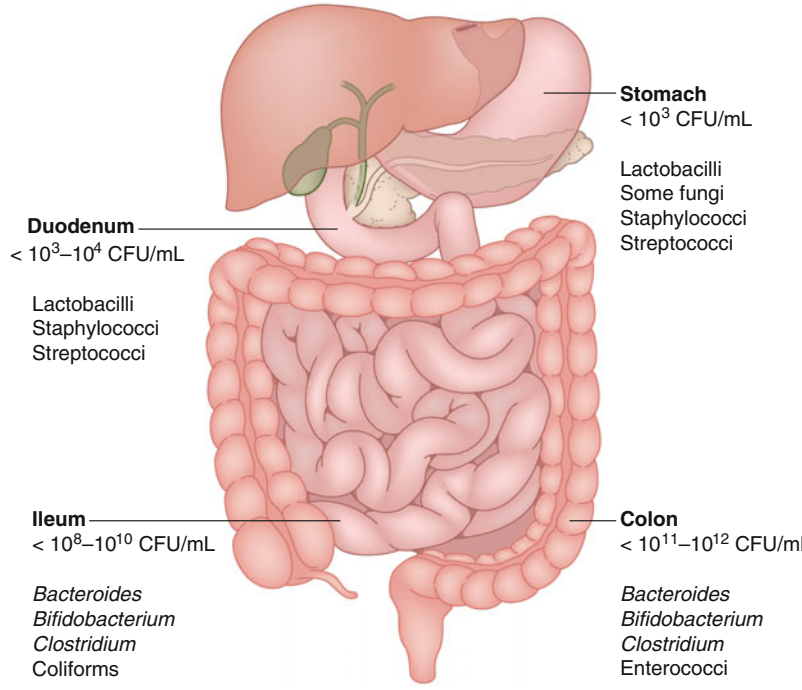

Fig. 3.1 Distribution of bacterial flora in the healthy human intestine (Reproduced from Cole and Ziegler [5])

intestine with coliform bacteria. The absence of the ileocecal valve is therefore a key prognostic factor in predicting outcome in short bowel syndrome, likely mediated by the role of bacterial overgrowth [8, 9]. As the postsurgical bowel undergoes adaptation, the bowel may dilate to increase absorptive surface area. This compensatory response may further result in an overly dilated, dysfunctional bowel that drives ongoing anatomic disadvantages. Therefore, patients with a shorter length of residual small intestine carry a higher risk for bacterial overgrowth [10].

Although congenital and postsurgical anatomic changes create the scaffolding for short bowel syndrome, the secondary alterations in gut motility further influence the bowel dysfunction that leads to intestinal failure. The enteric nervous system regulates gastrointestinal motility in both fasting and postprandial states. In the fasting state, motility is dominated by the migrating motility complex (MMC), a three-phase cycle that terminates in Phase III MMC. Phase III MMC activity originates in the proximal small bowel, generating progressive, short and intense contractions that migrate distally toward the ileum [11, 12]. This critical phase serves a housekeeping function, important in anterograde clearance of secretions, debris, and microbes. Extensive intestinal or predominantly ileal resection alters small intestinal motility as measured by shortened MMC cycles [13]. Furthermore, alterations in MMC have been associated with the development of bacterial overgrowth [13]. The intestinal microbiome is therefore altered in postsurgical states, influenced by perturbations in normal motility. Because the intestinal microflora plays a role in determining normal motility patterns, these alterations may spiral into downstream cycles of motility disturbances [12].

Aside from postsurgical short bowel syndrome, gastrointestinal motility disorders account for an important subset of etiologies in refractory intestinal failure [14]. Severe motility disorders, including chronic intestinal pseudo-obstruction, radiation enteritis, and systemic sclerosis, all have been shown to impact the MMC cycles [15–19]. Luminal stasis inherent in these disorders leads to bacterial overgrowth, which may further complicate the

Table 3.1 Factors contributing to microbiome alterations in intestinal failure

Anatomic
Dilated intestine
Foreshortened intestine
Stricture
Absence of the ileocecal valve
Motility:
Maladaptive bowel dilation
Primary/idiopathic motility disorder
Pharmacologic: loperamide, narcotic
Nutritional influences:
Enteral nutrition source
Parenteral nutrition, including parenteral lipid source
Malnutrition
Pharmacologic:
Acid suppression
Antibiotics
Antimotility agents
Narcotics

motility failure of the underlying disorder. A common pharmacologic treatment in diarrhea-predominant intestinal failure is the use of antimotility agents including loperamide, which may also alter MMC [20]. Disorders that result in a "two-hit" scenario, with significant alteration in both anatomy and motility, may result in more complicated outcomes in intestinal failure, and this may be mediated by the impact of bacterial overgrowth. Characteristic pediatric conditions, including long-segment aganglionosis or gastroschisis with atresia/short bowel syndrome, tend to result in more guarded prognosis and longer parenteral nutrition requirement [7].

Aside from underlying gastrointestinal anatomy and function, the host's nutritional state influences the small intestinal microbiome. The maldigestive and malabsorptive state, present in short bowel syndrome and pancreatic insufficiency, provides substrate that fuels the proliferation of bacterial populations that may not be present in health. Furthermore, malnutrition in itself may alter immunologic homeostasis and perturb physiologic checks and balances that regulate the microbiome [21]. Individual sources of enteral nutrition play a large influence in gut microbiota development, as is well established with the use of human milk, and has been demonstrated with variations in formula components, individual diets, and regional and cultural dietary and environmental influences. In contrast, the lack of enteral nutrition alters the function of the dynamic intestinal epithelial barrier, which plays a role in influencing the populations of individual bacterial strains that compose the microbiome [2, 22].

Pharmacologic alterations in intestinal pH may further impact the microbiome, contributing to bacterial overgrowth. Acid suppressive agents are commonly prescribed in to reduce the effects of post-resection gastrin hypersecretion, and to treat the suspected symptoms of gastroesophageal reflux disease or gastroduodenal hyperacidity. The Pediatric Intestinal Failure Consortium reported that 57 % of their patient cohort was exposed to proton pump inhibitor (PPI) therapy, and 69 % received histamine-2 receptor antagonist treatment [23]. PPI-induced alteration in small intestinal pH decreases bifidobacteria population and has been demonstrated to result in bacterial overgrowth [24]. Changes in the colonic pH alter population of both *Lactobacillus* and *Bacteroidetes* species and may foster *Clostridium difficile* infection [24]. Therefore, the relatively common practice of acid suppression prescription in the intestinal failure population may further impact dysbiosis, overgrowth, and associated sequelae.

Another pharmacologic necessity in the neonatal intestinal failure population is the use of broad-spectrum antibiotics. Antibiotics are prescribed commonly in neonatal and NICU care and have established effects on the developing infant microbiome [25]. The routine management of life-threatening surgical emergencies including necrotizing enterocolitis and volvulus requires systemic, broad-spectrum antibiotics to treat the effects of peritonitis and sepsis. Subsequent infectious events in the intestinal failure patient, namely, catheter-associated bloodstream infections, are relatively common and require intermittent courses of systemic antibiotics. These treatment regimens, although critical in the current standard of care in intestinal failure, may further lead to perturbations in gut flora.

Finally, the sine qua non in the definition of intestinal failure is the requirement for parenteral nutrition (PN), which, in itself, has been demonstrated to alter the intestinal microbiome through various mechanisms. In humans, isolation of the role of PN is challenging, based primarily on the multitude of clinical factors that cumulate in failure to tolerate adequate enteral nutrition. Therefore, the majority of data characterizing the effect of PN on microbial population changes derive from animal models. In both mouse and piglet models, PN exposure led to an expansion in *Proteobacteria* and *Bacteroidetes* species, with a decrease in *Firmicutes* [2, 26, 27]. This population shift leads to a proinflammatory state by affecting cytokine signaling within the intestinal immune system, theoretically leading to downstream mucosal and systemic inflammatory cascades that further influence the host and microbiome [26].

Taking these factors into account, there are multiple risk factors in the patient with intestinal failure that may conspire to create significant alterations in gut flora leading to dysbiosis and overgrowth. The complex interplay between anatomy, motility, enteral nutrient intake and malabsorption, epithelial barrier function, and mucosal/systemic inflammation summarizes a multifactorial pathogenesis, challenging the utility of a single therapeutic target for the downstream sequelae of microbial alterations in the intestinal failure patient. It is therefore not surprising that alterations in gut microbiome have been directly linked to outcome in intestinal failure. In a large retrospective series of pediatric patients with short bowel syndrome, the presence of bacterial overgrowth was predicated a significantly prolonged reliance on parenteral nutrition as compared to patients who did not have bacterial overgrowth [10]. In the evolving era of intestinal microbiomics, new techniques including 16s rRNA sequencing allow a detailed analysis of the intestinal flora in health and disease states. Both pediatric and adult patients with short bowel syndrome have been found to have uniquely different microbial patterns as compared to healthy controls, including description of decreased bacterial diversity in SBS with a population that favors a proinflammatory state [28–30]. Therefore, alterations in the microbiome in intestinal failure undoubtedly influence unique complications of the disorder and long-term outcomes.

Bacterial Overgrowth: Pathophysiology and Clinical Presentation

Small intestinal bacterial overgrowth manifests with predictable clinical presentations in the patient with intestinal failure (Table 3.2). The classic clinical presentation is driven by luminal bacterial fermentation of dietary carbohydrates, leading to bloating, gas, and malabsorptive stools. Furthermore, the bacteria interact with intraluminal bile acids, leading to a higher profile of deconjugated (and therefore inactive) bile acids. Bile acid-mediated micelle formation is secondarily impacted, resulting in fat malabsorption [5, 31]. Therefore, classic symptoms would include gas, bloating, watery diarrhea, and fat malabsorption. Bacteria may further lead to depletion or interference with intestinal disaccharidases, trypsin, and digestive enzymes, further driving osmotic diarrhea [32]. To the clinician, these symptoms are essentially identical to the malabsorptive symptoms associated with many anatomic etiologies of intestinal failure, namely, short bowel syndrome. Therefore, it may be impossible to distinguish the signs and symptoms of the patient's underlying intestinal failure from the secondary development of bacterial overgrowth. One should consider SIBO when the SBS patient has developed an increase in symptoms compared to baseline, especially in the setting of bowel dilation, and in later phase of adaptation. To that end, bacterial overgrowth should theoretically not be seen in the acute, postsurgical setting, characterized by fast transit, high output, and likely without adequate time for maladaptive colonization to incur [33].

Another luminal impact of small intestinal bacterial proliferation involves the downstream effects on micronutrient status. Decreased micelle formation impacts fat-soluble vitamin

Table 3.2 Clinical manifestations of dysbiosis and bacterial overgrowth in intestinal failure

Luminal:
Gastrointestinal symptoms related to carbohydrate fermentation:
Gas, bloating, distension, diarrhea
Toxin production: d-lactic acidosis
Fat malabsorption (bile acid deconjugation)
Micronutrient deficiencies:
B12, fat-soluble vitamins
Mucosal:
Mucosal inflammation/enteritis
Alterations in intestinal permeability and epithelial barrier function
Translocation/catheter-related bloodstream infection
Systemic:
Systemic inflammatory symptoms: arthritis, constitutional complaints
Liver disease
Sepsis/catheter-related bloodstream infection

absorption, which may result in vitamin A, D, and E deficiency states. Because vitamin K is produced by many strains of coliform bacteria, vitamin K deficiency and PT/INR prolongation is not commonly seen. Intestinal anaerobes compete with the host for vitamin B12, and therefore vitamin B12 levels may be low, compounded by the anatomic impact of ileal resection in short bowel syndrome. Monitoring of B12 status in the intestinal failure patient with overgrowth may be particularly challenging, as some strains of intestinal microbes may produce B12 analogues that interfere with conventional assays [34]. Methylmalonic acid, which is an established indicator for B12 status, has been shown to be elevated in a patient with SIBO, speculating that bacteria may lead to methylmalonic acidemia [35].

Intraluminal microbial toxin production may result in clinical sequelae, as is seen in the setting of D-lactic acidosis. This unique entity occurs when dietary carbohydrates are fermented by intestinal bacteria, leading to d-lactate production. In large quantities, the d-lactate crosses the blood-brain barrier and leads to D-lactic encephalopathy. Patients classically present with neurologic symptoms (altered mentation, slurred speech, ataxia) and laboratory evidence of an anion gap-positive metabolic acidosis [36]. D-lactic acidosis may occur through a few mechanisms, including high dietary carbohydrate intake (leading to overproduction of d-lactate from colonic flora), a dysbiotic state that favors the overpopulation of d-lactate-producing organisms, bacterial overgrowth, or short bowel syndrome. In the latter two scenarios, bacterial overpopulation and/or excessive carbohydrate malabsorption fuels microbial fermentation and secondary lactate production. As luminal pH declines, this milieu favors the survival of d-lactate-producing species, including *Lactobacillus fermenti*, *L. acidophilus*, and *Streptococcus* [36]. D-lactic acidosis should be considered in any patient with intestinal failure/short bowel syndrome that presents with changes in mental status. Diagnosis is traditionally confirmed with laboratory analysis of d-lactate level in plasma. Treatment recommendations include correction of acidosis, dietary carbohydrate restriction, and initiation of oral/enteric antibiotics. Akin to D-lactic acidosis are clinical syndromes that have been described by other by-products of bacterial carbohydrate fermentation, including ethanol and ammonia [33].

An important and evolving area of both clinical and laboratory investigation is the spectrum of mucosal inflammatory disorders in intestinal failure. Enteritis is a recognized complication in short bowel syndrome, and it has been associated with the occurrence of bacterial overgrowth [10, 37]. The spectrum of mucosal inflammatory disease is variable, and may include patchy visual or microscopic inflammation, anastomotic ulcerations, and Crohn's-like ulcers with severe, chronic inflammation, typically without granulomata [38–40]. Although the pathogenesis of this complication is not well understood in intestinal failure, the interaction between luminal bacteria and mucosa in other disorders including inflammatory bowel diseases may have overlapping mechanisms to intestinal failure-associated enteritis [41–43]. Facultative anaerobes produce endotoxin, and aerobes produce proteolytic enzymes, which may have direct effects on mucosal injury and inflammation [5, 44]. As has

previously been discussed, changes in intestinal microbiome related to TPN may further drive disturbances in the epithelial barrier and influence proinflammatory immunologic pathways.

Luminal and mucosal disease that is influenced by the microbiome may dictate some of the more notorious extraintestinal complications in intestinal failure. Disruption of the epithelial barrier function coupled with luminal bacterial overpopulation may trigger bacterial translocation and spawn septic events including catheter-related bloodstream infections [45–47]. Cole et al. described a high incidence (0.80) of bloodstream infections in a cohort of ten infants with intestinal failure, and the presence of bacterial overgrowth (confirmed by breath testing) increased odds for infection by sevenfold, without evidence of altered small intestinal permeability [48].

As the host inflammatory state is turned on, either by overt bacteremic events or subclinical mucosal injury with or without endotoxemia, patients may develop other systemic manifestations attributed to overgrowth. Rash, arthritis, and fatigue may occur. Utilizing the model of inflammatory bowel disease, the mucosal inflammatory state carries a comorbid risk for venous thrombosis [49, 50]. Furthermore, small bowel bacterial overgrowth has recently been linked to a higher risk for deep vein thrombosis [51]. One may extrapolate that the microbial-derived inflammatory state contributes to the high burden of catheter-associated venous thrombosis in patients with intestinal failure [52].

No discussion involving the impact of the microbiome in the patient with intestinal failure is complete without mention of its implicated role in liver pathogenesis. Sepsis events, possibly influenced by overgrowth and mucosal injury, have been well associated with the severity and progression of PN-associated liver disease [53]. From a mechanistic level, dysbiosis and increased intestinal permeability may lead to increased absorption of microbe-associated molecular pattern, leading to Kupffer cell activation through Toll-like receptor signaling. These pathways, and the luminal microbial patterns, are further influenced by parenteral lipid emulsions, in that soy-derived plant sterols may favor the overpopulation of proinflammatory taxa [54, 55]. Therefore, parenteral lipid emulsions coupled with dysbiosis and overgrowth may play a key role in the multifactorial pathogenesis of PN-associated liver disease.

Diagnostic Testing

In the present era, confirmatory diagnostic testing for bacterial overgrowth is wrought with challenges, and therefore empirical therapy is often employed in clinical practice. Because a definition of SIBO requires greater than 10^5 CFU/mL of intestinal fluid, duodenal/jejunal aspirate is considered a theoretical gold standard. Fluid can be obtained relatively easily by standard endoscopic techniques. The proceduralist should be careful to avoid suctioning fluid from the oropharynx or stomach prior to duodenal intubation to minimize contamination, and sterility may be improved by passing a sterile suction catheter through the endoscope channel. The procedure itself is complicated by relative expense, and the requirement for procedural sedation or general anesthesia. Gutierrez et al. reported a high yield of positive diagnostic aspirates for SIBO in their series of 57 patients with intestinal failure that underwent diagnostic endoscopy, in which 70% of patients were found to have overgrowth (defined as $>10^5$ CFU/mL fluid) [4]. Challenging this approach, however, is the relative difficulty in culturing many species of intestinal microbiomes, including anaerobes. Clinical laboratories may have varied degrees of expertise in this technique. Therefore, quantitative results may underestimate true luminal bacterial load, and speciation may not accurately reflect the pathogenic spectrum [56]. Nevertheless, this technique is used by many centers to reinforce clinical suspicion and decipher appropriate antibiotic treatment choices.

Hydrogen breath testing (HBT) is a less invasive modality that utilizes exhaled hydrogen gas as a by-product of luminal bacterial carbohydrate metabolism. Various ingested substrates have been evaluated including glucose, lactulose, and xylose. A positive test results in a change in

exhaled hydrogen by >10 ppm compared to baseline. Unique features in patients with short bowel syndrome may complicate interpretation of the tests. Most importantly, alterations in gut transit, either fast or slow transit, impact results. Similarly, the patient with a short small bowel length and colon intact may register a "positive" test based on substrate interaction with colonic flora. In addition, some species of intestinal bacteria preferentially produce methane, which may not register in the HBT. Finally, cooperation may be limited in younger pediatric patients with intestinal failure leading to inadequate breath collection.

A compelling future direction in the clinical assessment of microbial profile employs 16s ribosomal RNA (rRNA) gene sequencing. This technique allows extensive microbial profiling of relatively easy-to-obtain biological samples, including stool or intestinal mucosal biopsy. Engstrand et al. recently reported on 11 pediatric patients with IF/SBS who had 16s rRNA sequencing of fecal samples. They found an abundance of facultative anaerobic *Enterobacteriaceae* in children on PN compared to those weaned from PN and healthy siblings, a microbial profile similar to patients with inflammatory bowel disease and NEC [30, 57]. Thus, 16s rRNA sequencing may provide detailed characterization of the dysbiotic microbiome in intestinal failure, offering further insight on pathogenesis and potential treatments.

Because of challenges in accuracy and reliability of objective diagnostic testing for SIBO, intestinal rehabilitation centers frequently resort to utilization of empiric antibiotics when clinical suspicion is warranted. This widely accepted practice continues to carry risk for antimicrobial resistance and microbial selection and may foster worsening dysbiosis.

Finally, when bacterial overgrowth is suspected, one should consider evaluations for underlying etiology and/or sequelae. Structural evaluations utilizing gastrointestinal contrast (e.g., upper gastrointestinal series with small bowel follow-through) may reveal stricture or pathologically dilated loops of bowel. Endoscopy with mucosal biopsy may demonstrate mucosal inflammation. Micronutrient surveillance should be performed with attention to vitamin B12 and other vitamin levels that are influenced by microbial overgrowth.

Treatment

Oral/enteric antibiotic treatment remains the mainstay of therapy in bacterial overgrowth. Initiation of antibiotic treatment should be considered when the patient has digestive symptoms (gas, bloating, diarrhea, early satiety, distension) that are increased compared to clinical baseline, especially in the setting of dilated bowel, diagnostic confirmation of SIBO, or previous treatment response to antibiotics. Antibiotic therapy may also be considered as an adjunct treatment in intestinal failure-associated enteritis, recurrent catheter-related bloodstream infections, or anastomotic ulcerations – although these treatment pathways are experience based without conclusive clinical evidence supporting benefit of therapy. The decision to initiate antimicrobials should be weighed against the potential consequences, including further cycles of dysbiosis, microbial selection, and resistance patterns.

Selection of the appropriate antibiotic remains largely empirical, with center-to-center variation in prescription patterns. The ideal antimicrobial choice would be largely active in the intestinal lumen only, with little systemic absorption, and have penetrance toward typical offending coliform and anaerobic bacteria, but carry low risk of side effect or antibiotic resistance. Medications that target anaerobes include metronidazole and nitazoxanide. Rifaximin and Amoxicillin/clavulanic acid both have a relatively large spectrum of activity, including aerobic and anaerobic gram-negative and gram-positive species [58–60]. Augmentin carries the additional benefit of a promotility agent; therefore, it may have a dual therapeutic benefit. Rifaximin is nonabsorbable and has primarily bacteriostatic properties; there is less concern about development of microbial resistance patterns in comparison to standard bacteriocidal alternatives [33]. Ciprofloxacin affects coliform bacteria including enterococcus and anaerobes. Antibiotics that target gram-negative

aerobes include aminoglycosides (gentamicin and tobramycin), sulfamethoxazole/trimethoprim (Bactrim), and cephalosporins [3].

Antibiotics may be prescribed for a single 1–2 week courses, or may be cycled. Cycling patterns vary, but typically include utilization of an antibiotic with anaerobic penetrance (e.g., metronidazole), followed by an antibiotic with targeted gram-negative penetrance (e.g., gentamicin), with a gap either in between or following back-to-back courses. The potential benefits of rifaximin for small bowel bacterial overgrowth in other gastrointestinal disorders, including irritable bowel syndrome, make this a favorable choice and may be incorporated into treatment protocols [61]. When available, duodenal aspirate and culture may inform antibiotic selection strategies.

Treatment of dysbiosis and overgrowth would ideally be targeted at restoring normal bacterial homeostasis, rather than broadly eliminating potential overpopulated strains. Therefore, the utilization of probiotics and prebiotics has theoretical benefit in this arena. Probiotic therapy, that is, the luminal inoculation of live strains of theoretically beneficial bacteria, has many potential benefits in gastrointestinal and systemic human disease. Probiotics may induce effects by producing bacteriocins that affect local microorganism populations, competing for physical space and nutrients in the mucosa, and improving epithelial border function, immune response, and gut adaptation [62]. Current available probiotic therapies largely include *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces* strains. Probiotics are largely utilized in inflammatory and functional gastrointestinal disorders with mixed reported benefit [63–65]. Interpreting the results of clinical studies involving probiotic therapy is challenging, based on variant microbial strains and concentrations, as well as analysis of benefit in the setting of largely heterogeneous groups of disorders. These challenges exist in translating the potential benefits of probiotic therapy in the patient with intestinal failure. Various reports have demonstrated benefit of probiotic therapy in short bowel syndrome and intestinal failure [66–68]. However, bacteremia with lactobacillus and other probiotic strains have been reported in patients with central venous catheters [69–71]. Akin to the principles behind probiotic therapy, a recent case report describes the successful use of fecal microbiota transplant to treat recurrent D-lactic acidosis in a child with short bowel syndrome [72].

Aside from direct inoculation of live bacteria to alter flora, prebiotic therapy aims to "feed the gut" with substrates that are conducive to the proliferation of symbiotic bacterial strains. The administration of fructo-oligosaccharides, human milk oligosaccharides, and inulin-type fructans may help to improve intestinal barrier function and fuel the development of appropriate flora.

More global management strategies in approaching the patient with intestinal failure and bacterial overgrowth may target underlying etiology, or secondary complications. As has been discussed, the patient may likely have a dilated, dysfunctional bowel, with secondary associated dysmotility. The use of promotility agents, including Augmentin, cisapride, and erythromycin, may be beneficial [73–75]. It should be mentioned that cisapride carries an established risk of QTc prolongation and sudden cardiac death; therefore, careful consideration and monitoring should occur if this therapy is considered. When bowel dilation has evolved and the intestinal architecture promotes stasis and failed enteral advancement, then autologous bowel reconstruction should be considered. Serial transverse enteroplasty and other "lengthening" procedures may induce significant effects by improving luminal diameter and restoring function, as opposed to the measured increase in length alone. Therefore, these surgical interventions may be required in refractory dysbiotic states including recurrent D-lactic acidosis [76]. Finally, management of intestinal failure-associated enteritis presentations, from "short bowel-associated colitis" to Crohn's-like ulcerations, may require combined approach of antimicrobial management of the overgrowth, targeted mucosal anti-inflammatory therapy, or systemic immunosuppressive agents. At present, the pathogenesis of this complication is not well

understood. However, as our understanding of the significance of alterations in the microbiome in various intestinal inflammatory disorders evolves, we can speculate that future directions in the treatment of the intestinal failure patient may involve targeted treatment of mucosal inflammation to address a theoretical link between the luminal microbiome and the systemic complications of the host.

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Intestinal Failure-Associated Liver Disease

4

Mikko P. Pakarinen and Annika Mutanen

Abbreviations

FGF 19	Fibroblast growth factor 19
FXR	Farnesoid X receptor
ICV	Ileocecal valve
IF	Intestinal failure
IFALD	Intestinal failure-associated liver disease
IL	Interleukin
LPS	Lipopolysaccharide
PN	Parenteral nutrition
SBS	Short bowel syndrome
TLR4	Toll-like receptor 4
TNFα	Tumor necrosis factor α

Introduction

Intestinal failure (IF) has been defined as extensive malabsorption secondary to intestinal dysfunction, which results in the inability to sustain adequate energy and/or water balance without parenteral support for maintenance of health and/or growth [1]. An increasing number of infants and children with IF are supported by parenteral nutrition (PN) worldwide [2]. The most common causes of IF include short bowel syndrome secondary to necrotizing enterocolitis, intestinal atresia, malrotation-related midgut volvulus and gastroschisis, and primary intestinal motility disorders such as Hirschsprung disease and chronic intestinal pseudo-obstruction [2, 3]. Majority of the patients are able to wean off after variable duration of PN, whereas others remain PN dependent permanently. The connection between PN and liver disease has been well recognized for several decades. Early in the disease course and especially in newborns, the clinical hallmark of intestinal failure-associated liver disease (IFALD) is cholestasis, which may rapidly progress to biliary cirrhosis and liver failure [4]. Although impaired bile flow is a central feature in IFALD, other biochemical and histological derangements in liver function often persist even if resolution of cholestasis is achieved. IFALD has replaced previously used terms PN-associated cholestasis or PN-associated liver disease as it has become increasingly apparent that also other pathophysiological factors besides PN, such as compromised intestinal function, essentially contribute to the development and maintenance of liver disease in patients with IF [5]. Moreover, recent studies have demonstrated that histological liver injury in IFALD has a high tendency to persist, and it may even progress after weaning off PN [6, 7].

M.P. Pakarinen (✉) • A. Mutanen
Section of Pediatric Surgery, Pediatric Liver and Gut Research Group Helsinki, Children's Hospital, University of Helsinki and Helsinki University Hospital, Stenbackinkatu 11, P.O. Box 281, Helsinki 00029 HUS, Finland
e-mail: mikko.pakarinen@hus.fi

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Epidemiology

The incidence of IFALD varies greatly across different studies due to variable definitions. According to a recent systematic review, approximately half of children receiving PN for longer than 14 days developed IFALD, while no apparent changes in the incidence has occurred during the last decades [8]. In a recent prospective nationwide study, incidence of IFALD was 63 % among neonates and 27 % among children receiving PN beyond 28 days [9]. IFALD continues to be the major cause of mortality and the leading cause for intestinal transplantation in pediatric IF [10]. In a recent large North American survey, 75 % of the children with IF developed cholestasis, and the cumulative chances for survival were significantly decreased in those with cholestasis, 79 % vs 95 % at 1 year and 73 % vs 88 % at 3 years [2]. IFALD leads to end-stage liver disease in approximately 5 % of children [11]. In children with IF, mortality rate of end-stage liver disease approaches 100 % within 1 year of diagnosis if weaning off PN is not achieved or intestinal transplantation (with or without liver) is not performed [12].

Definition

IFALD can be defined as hepatobiliary dysfunction and/or histological liver injury, which develops during PN delivered for compromised bowel function and related IF without other causes for the liver disease. Usually IFALD presents as cholestasis and encompasses both acute and chronic derangements of hepatobiliary function with a wide clinical spectrum ranging from mild histological changes and biochemical alterations to end-stage liver failure with cirrhosis, portal hypertension, ascites, and coagulopathy [13]. There are no clear generally accepted criteria for IFALD, and the diagnosis is often made on clinical grounds in a PN-dependent child with IF, who develop signs of liver dysfunction. The diagnosis is usually based on a persistent elevation of liver biochemistry while ruling out other potential causes of liver disease [4]. More than 1.5-fold increase above the upper normal limit for at least two of the following parameters: conjugated bilirubin, alanine aminotransferase (ALT), and glutamyl transferase (GT) have been used by several authors [9, 14]. Another commonly employed criteria include the presence of conjugated bilirubin $\geq$ 34 μmol/l in an infant with duration of PN $\geq$ 14 days [8]. In many patients only subtle changes in liver biochemistry occur, despite significant histological liver injury [6]. No standardized generally accepted histological criteria for IFALD are available, although the severity of IFALD has been classified based on laboratory values, clinical findings, and liver histology [15].

Liver Histology in IFALD

During PN delivery, liver histology is abnormal in the majority of children with IF (Table 4.1). Cholestasis and portal inflammation are the first histopathological changes, which are observed together with fibrosis in the majority of patients. Steatosis becomes gradually more common after prolonged duration of PN and with increasing patient age [6, 16]. Ductal proliferation may accompany intracellular, canalicular, and ductular cholestasis together with portal inflammation consisting of neutrophils and lymphocytes [6]. Cholestasis is closely associated with portal inflammation, outlining the close relationship of cholestasis and inflammation in the initial pathogenesis of liver injury in IFALD. Histological cholestasis is more common among premature infants in relation to those born full-term and may develop in less than 2 weeks of PN delivery [17]. In a study on children with IF, abnormal liver histology was found in 94 % of patients after a mean PN duration of 6 years, while only 50 % showed abnormal liver biochemistry values [6]. Overall, 88 %, 50 %, 38 %, 29 %, and 38 % of the children displayed histological liver fibrosis, steatosis, cholestasis, ductal proliferation, and portal inflammation, respectively, while 94 % had any histological abnormalities. The majority of the patients had significant fibrosis corresponding Metavir stage 2 or greater, while equal amounts

of micro- and macrovesicular steatosis with no associated Mallory body formation or apoptosis were observed. Fibrotic change of the liver may progress to porto-central scarring and cirrhosis, which occurs rapidly in occasional children. The degree of liver fibrosis and steatosis is interrelated in children with IF, suggesting their linked pathogenesis [16]. Among 79 children with IF referred to intestinal transplantation, 58 % had precirrhotic changes or established cirrhosis [18]

Abnormal histological liver fibrosis and steatosis persist after weaning off PN, despite diminishing cholestasis and portal inflammation. In a cross-sectional follow-up study on patients with pediatric onset IF, abnormal liver histology was found in 77 % of patients, who had weaned off PN an average of 8.8 years before after receiving PN for an average of 3 years [6]. Of them, 60 % had Metavir stage 2 fibrosis, 45 % displayed steatosis, none had cholestasis, 10 % had ductal proliferation, and 9 % had portal inflammation, while only 18 % of the patients showed abnormal liver biochemistry. Other retrospective studies and case reports also suggest that liver histology remains abnormal and may even continue to progress after weaning off PN [17]. Clearly, further studies are needed to define whether the persistent histological liver injury represents a

Table 4.1 Studies on liver histology in children with intestinal failure

Reference	Population		Diagnoses	Duration of PN	Liver histology		
		n		Mean (mo)	Cholestasis (%)	Fibrosis (%)	Steatosis (%)
Rodgers (1976)	Infants on PN	11	IF and others[a]	NR	100	NR	NR
Postuma (1979)	Neonates on PN	14	IF and others[a]	NR	86	86	NR
Cohen (1981)	Infants on PN	31[b]	IF and others[a]	NR	61	35	68
Dahms (1981)	Infants on PN	11	IF and others[a]	2.5	100	91	NR
Moss et al. [17]	Infants on PN	36[b]	IF and others[a]	NR	73	30	NR
Misra (1996)	Children on PN	8[c]	IF and others[a]	NR	13	50	NR
Loff (1999)	Neonates on PN	10	IF and others[a]	NR	100	NR	NR
Zambrano (2004)	Neonates on PN	24[b]	IF and others[a]	1	79	71	29
Fitzgibbons (2010)	Children on PN	83	IF and others[a]	4.7[d]	NR	89	NR
Peyret (2011)	Children on PN	18	IF	8	39	94	39
Naini (2012)	Children and adults on PN	89[c]	IF and others[a]	30	81	96	39
Diaz (2013)	Children on PN	62	IF	12.5[d]	NR	58	NR
Mutanen et al. [6]	Children with IF	38	IF	49			
	On PN	16		74	38	88	50
	Weaned off PN	22		35	0	64	45

IF intestinal failure, *n* number of patients, *NR* not reported, *PN* parenteral nutrition, % percentage of patients

[a]Underlying diagnoses other than intestinal failure, for example, congenital heart disease, prolonged endotracheal intubation and intensive care, sepsis, bronchopulmonary dysplasia, esophageal atresia, pancreatitis, and ileus were included in the study population

[b]Autopsy samples

[c]Some patients with liver transplantation

[d]Median

potentially progressive and destructive disease process, because an increasing number of children with IF are successfully weaned off PN with a long life expectancy.

Risk Factors and Preventive Measures

Intestinal surgery markedly increases the risk of IFALD in neonates and children requiring PN [19–21]. Etiology of IFALD is most likely multifactorial. Accordingly, various clinical risk factors have been linked with the development of IFALD. In addition to intestinal pathology, the most important clinical risk factors include duration, amount and composition of PN, enteral nutrient deprivation, remaining small bowel length, absence of the ileocecal valve (ICV), septic episodes, intestinal bacterial overgrowth, and young gestational age (Table 4.2). Many of these risk factors are modifiable offering possibilities for prevention and treatment of IFALD.

Duration of PN is a central risk factor of IFALD and associated histological liver injury. The frequency of biochemical liver dysfunction is linearly related to PN exposure. Duration of PN correlates with the frequency of histological cholestasis and fibrosis in infants, while histological liver fibrosis and steatosis progress in parallel with increasing duration of PN exposure in older children [6, 17]. Whenever tolerated, provision of tolerated enteral nutrition during PN delivery offers an effective way to prevent and even reverse IFALD as enteral nutrient deprivation promotes mucosal atrophy and epithelial barrier dysfunction [22]. Enteral feeding activates meal-stimulated secretion of bile, bile acids, and pancreatic fluid along with a plethora of gut-derived hormones and growth factors including glucagon-like peptides 1 and 2 supporting epithelial integrity and intestinal motility. Excess of parenteral energy in the form of either fat, glucose, or amino acids has been associated with pathological changes in liver biochemistry and histology, including elevated transaminases, steatosis, and cholestasis [11]. Cyclic infusion of PN with the support of tolerated amount of enteral feeds during infusion breaks may reduce the risk of liver complications [23]. This practice has been shown to result in reduction of serum liver enzymes and conjugated bilirubin, and it also helps to avoid hyperinsulinemia and fat deposition in the liver [11].

Composition of PN lipids and their excessive delivery have a central role in the development of IFALD, and reduction of overall parenteral fat is a clinically applied approach when signs of IFALD occur to prevent further liver damage. Reduction of soy oil-based lipid emulsion in PN to 1 g/kg/day twice a week has been shown to significantly reduce bilirubin levels in neonates [24]. Soy oil-based PN lipid emulsions in particular have been regarded as a significant clinical risk factor of IFALD. They contain high concentrations of polyunsaturated omega-6 fatty acids and plant sterols such as sitosterol, stigmasterol, avenasterol, and campesterol and low contents of an important antioxidant α-tocopherol. Alternative lipid emulsions containing significant amounts of olive and/or fish oil have largely replaced purely soy oil-based lipids in Europe. Olive oil is rich in omega-6 fatty acids and (omega-9) oleic acid, a monounsaturated fatty acid that is less prone to lipid peroxidation than polyunsaturated fatty acids [25].

Table 4.2 Main clinical risk factors of intestinal failure-associated liver disease

Surgically treated intestinal pathology Enteral nutrient deprivation
Parenteral nutrition associated factors
Prolonged duration Plant sterols containing lipid emulsion Excess lipid provision
Excess energy provision
Low omega-3/omega-6 fatty acid ratio
Septic complications
Bacterial translocation
Central line-associated blood stream infections
Intestinal factors
Short remaining small bowel
Loss of ileocecal region
Loss of ileum Bacterial overgrowth Intestinal inflammation
Young gestational age

Olive oil contains less plant sterols and soy oil, and their distribution differs by olive oil containing markedly less stigmasterol [26]. Fish oil-based emulsions are rich in omega-3 fatty acids and α-tocopherol and are devoid of plant sterols in contrast to vegetable oil-based lipid emulsions. In general, the downstream products of omega-6 fatty acids through arachidonic acid are potent proinflammatory eicosanoids, including leukotrienes, prostaglandins, and thromboxane A2. In contrast, omega-3 fatty acids are thought to have hepatoprotective potential via production of less proinflammatory eicosanoids and pro-resolving mediators of inflammation through eicosapentaenoic and docosahexaenoic acids. PN lipid emulsions containing plant sterols and their increased serum concentrations have been repeatedly linked with biochemical and histological liver injury in IF. Serum levels of plant sterols markedly increase in children during soy oil- and olive oil-based PN in parallel with biochemical and/or histological evidence of IFALD [9, 27, 28]. A number of studies have indicated that the use of fish oil either alone or in combination with other lipid emulsions is an effective way to decrease occurrence and enhance recovery from IFALD-associated cholestasis, although adequately powered randomized controlled clinical trial to test this hypothesis has not been performed [5]. At present, contribution of lower overall lipid dose, different fatty acid profile, higher α-tocopherol content, and lesser plant sterol content to the advantageous clinical experiences with the fish oil-based lipid emulsions remains unclear. In addition to limited overall PN lipid load, PN lipid emulsions with low soy oil-derived omega-6 fatty acid and plant sterol contents, for example, by combining lipid emulsions based on olive and fish oil has been adopted increasingly in order to prevent IFALD [11, 29]. Active surveillance of serum fatty acid profiles, fat-soluble vitamins, and plant sterol concentration along with biochemical markers of liver function enables meaningful adjustments of the lipid source and vitamin supplementation to avoid essential fatty acid deficiency, shortage of fat-soluble vitamins, as well as plant sterol overload [29].

Unsurprisingly, septic infections are a well-recognized and a significant risk factor of IFALD. Systemic bacterial infections disturb hepatic function and biliary secretion by numerous mechanisms, which induce cholestasis. Lipopolysaccharides (LPS) and endotoxins act as inflammatory signals that reduce gene and protein expression of bile transporters either directly or by activating cytokine production through toll-like receptor 4 (TLR4) in Kupffer cells [30]. IFALD-associated cholestasis is more common in children with recurrent septic episodes, originating either from central line infections or bacterial translocation from the intestine. The number of septic episodes correlates positively with liver fibrosis in children with IF and predicts elevated bilirubin levels in neonates with surgical SBS [6, 31]. Sepsis episodes frequently precede development of cholestasis. Primary intestinal motility disorders and massive intestinal resection leading to IF favor development of intestinal bacterial overgrowth through frequent loss of the ICV, abnormal bowel dilatation, and impaired intestinal motility patterns. Altered intestinal microbiota may promote translocation of bacteria and their antigens through inflamed and leaky intestinal epithelium into the portal circulation. Accordingly, in patients with pediatric onset IF, altered intestinal microbiota composition associates with histological liver injury, while loss of the ICV, predisposing to small intestinal overgrowth of colonic bacteria, has been clinically linked with the progression of liver fibrosis [6, 32]. The contribution of intestinal microbiota to development of IFALD is supported by successful prevention of cholestasis with erythromycin in PN-dependent neonates [8]. Effective control of central line-derived blood stream infections by antimicrobial lock therapies and standardized care protocols offers a potential way to prevent IFALD. Surgical treatment of obstructive short bowel pathology predisposing to bacterial overgrowth seems to be equally important. Strictures and excessive bowel dilatation associated with stasis should be treated operatively to prevent bacterial overgrowth and to optimize bowel function [3, 31].

The length of the remaining small intestine is a powerful prognosticator of IFALD-associated cholestasis and histological liver fibrosis in pediatric IF [6, 33]. Extremely short small bowel remnants correlate with prolonged PN dependence and may predispose to gut-derived infections favoring development of IFALD indirectly. Massive small intestinal resections are likely to promote IFALD also directly by disturbing gastrointestinal physiology and the gut-liver axis more profoundly than more limited resections.

Newborns, particularly those with a young gestational age, have an increased risk of IFALD [11, 19]. In the newborn, immaturity of the liver is associated with reduced bile salt pool and incompletely developed molecular mechanisms responsible for biliary secretion and bile acid uptake [34]. The newborn hepatobiliary physiology is likely to contribute to the high risk of IFALD in the neonatal period. In addition to liver immaturity, premature babies are exposed to multiple risk factors of IFALD, which include increased vulnerability to sepsis, defective intestinal propulsive motility predisposing to feeding intolerance, relatively high parenteral fat and glucose dosage to meet energy needs, and requirements for continuous rather than cyclic PN infusions.

Pathogenesis of IFALD

Intestinal pathology is a major prognosticator of IFALD in neonates and children, who require prolonged PN, suggesting that compromised bowel function essentially contribute to the IFALD pathogenesis [19, 20]. Accordingly, in mice, both administration of PN and impaired intestinal barrier function are required for development of cholestatic liver injury [35]. In this mouse model, pharmacologically induced epithelial barrier dysfunction in unresected intestine leads to LPS translocation to the portal circulation, which in combination with soy oil PN lipid emulsion causes biochemical cholestasis and histological liver injury by activating Kupffer cell expression of proinflammatory cytokines interleukin-1 (IL-1), IL-6, and tumor necrosis factor α (TNFα) and profibrotic transforming growth factor ß through TLR4 signaling. Neither LPS translocation nor PN alone caused liver injury, which was attenuated after suppression of enteric microbiota with broad-spectrum antibiotics or ablation of TLR4 signaling. Further studies in this IFALD mouse model showed that infusion of PN lipid emulsion containing plant sterols (derived from soy oil) or stigmasterol alone in combination with increased LPS permeability produced biochemically verified IFALD through stigmasterol-mediated inhibition of canalicular bile acid (*ABCB11*), bilirubin (*ABCC2)*, and sterol (*ABCG5/G8*) transporter expression by antagonizing their upstream regulators nuclear receptors farnesoid X receptor (FXR) and liver X receptor (LXR) [36]. Inhibition of hepatocyte bile and sterol transporters was reversed after removing plant sterols from PN using fish oil-based lipid emulsion, antibiotic suppression of enteric flora, and TLR4 ablation. Furthermore, stigmasterol and LPS induced in vitro transcription of proinflammatory cytokines (IL-1ß, IL-6, and TNFα) in naive mouse macrophages. In cultured hepatocytes not only stigmasterol but also other plant sterols such as sitosterol and campesterol antagonize FXR and expression of its target genes, which control bile acid homeostasis and biliary secretion in the liver [36–38]. These experimental data suggest that parenteral plant sterols and translocated LPS or other bacterial antigens following loss of intestinal epithelial barrier integrity synergistically promote IFALD. Plant sterols and LPS activate hepatic Kupffer cell expression of proinflammatory cytokines thorough TLR4 signaling and suppress hepatocyte expression of canalicular bile transporters by antagonizing nuclear receptor signaling, which induces cholestasis and hepatic accumulation of plant sterols and bile acids. Some of the above reviewed mechanisms unraveled in mice may be translatable to IFALD observed in humans. Patients with pediatric onset IF show increased serum concentrations of IL-6 and TNFα, and IL-6 levels correlate positively with histological cholestasis, suggesting that proinflammatory status is linked with IFALD-associated cholestasis also in humans [7]. A number of clinical studies also support the role of

PN plant sterols and compromised intestinal barrier function in the pathogenesis of IFALD. The possible mechanisms of IFALD pathogenesis are outlined in Fig. 4.1.

Provision of PN lipid emulsions containing plant sterols and their simultaneously increased serum concentrations have been repeatedly linked with biochemical and histological liver

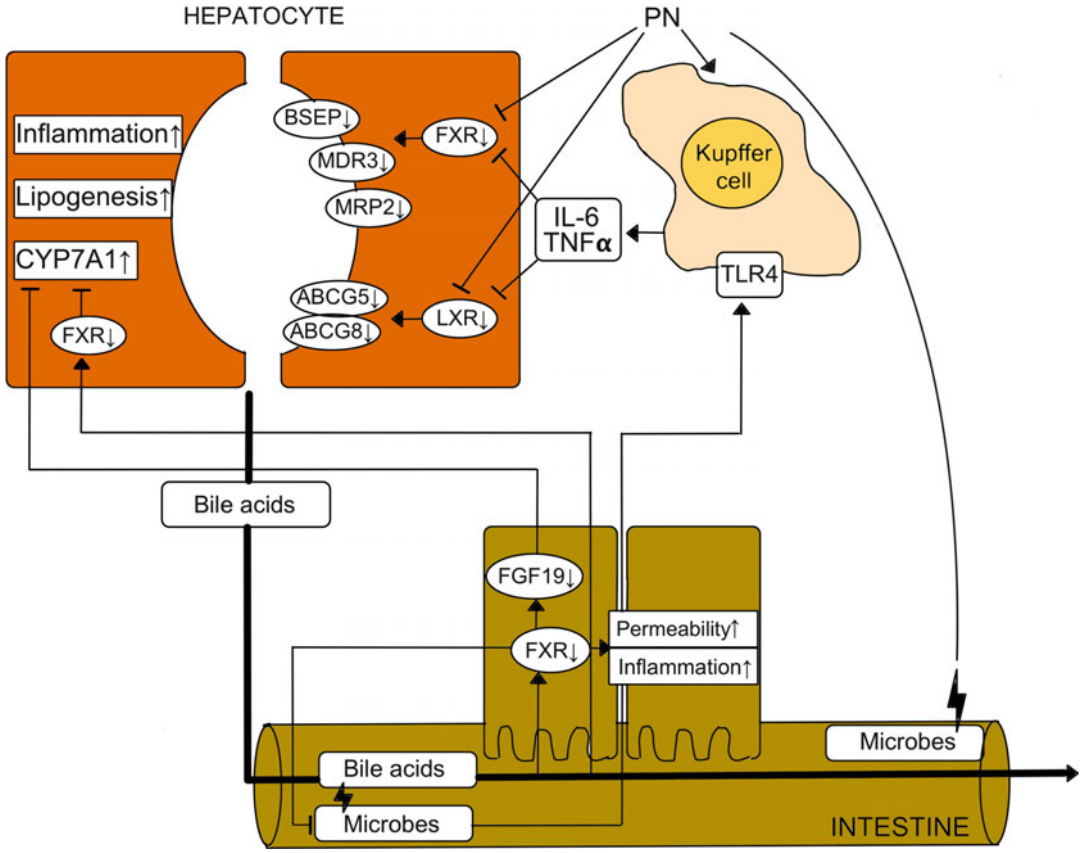

Fig. 4.1 Possible pathogenic mechanisms of IFALD. Plant sterols derived from vegetable oil-based PN lipid emulsion antagonize nuclear receptors FXR and LXR, which results in decreased expression of their target genes encoding canalicular bile acid (*ABCB11*), phospholipid (*ABCB4*), bilirubin (*ABCC2*), and sterol (*ABCG5*/*G8*) transporters, impairing bile flow. Defective biliary secretion predisposes to injurious detergent effects of bile acids and further accumulation of plant sterols to hepatocytes. Plant sterols activate liver macrophages directly and may promote selection and overabundance of specific intestinal bacterial species. IF-associated intestinal epithelial barrier dysfunction allows translocation of LPS and other bacterial antigens to the portal vein, activating liver macrophages through TLR signaling, which also occurs in response to central line-derived bacteremia. Proinflammatory cytokines including IL-1, IL-6, and TNFα produced by activated liver macrophages inhibit expression of canalicular bile transporters. LPS may inhibit protein and gene expression of biliary transporters also directly. Following their biliary secretion, bile acids enter the intestine, where they undergo microbial modifications affecting their absorbability and ability to activate target receptor FXR after being actively absorbed to the ileal enterocytes. Surgical removal of the ileum and subsequent malabsorption of bile acids due to loss of their active ileal absorption site reduces intestinal FXR activation, which result in decreased transcription of FGF 19. Altered intestinal microbiota chemically modifies bile acids altering their ability to active nuclear target receptor FXR. Defective intestinal FXR induction may interfere with prevention of intestinal bacterial overgrowth, inflammation, and barrier dysfunction. Interrupted enterohepatic circulation of bile acids decreases hepatic FXR activation, which together with defective ileal FGF 19 secretion leads to activation of *CYP7A1*, the rate-limiting enzyme in the bile acid synthesis. Impaired FXR-FGF 19 axis has potential to promote liver injury also by inducing lipogenesis and inflammatory responses in the liver. See text for references

injury in children and adults [39]. Experimental studies have shown that intravenously administered plant sterols accumulate in the liver reflecting their serum concentrations while attenuating bile flow [40]. Normally, only small amounts (<5 %) of dietary plant sterols are absorbed from the intestine, and their serum levels remain low [39]. Markedly increased serum concentrations of stigmasterol and its close structural homologue avenasterol have been shown to correlate positively with histological portal inflammation and cholestasis in PN-dependent children [27]. Biochemical cholestasis, high serum concentrations of stigmasterol and avenasterol, and histological cholestasis were interrelated, while the magnitude of increase in serum plant sterol concentrations in children was similar to those reported in animal models. Moreover, in PN-dependent neonates with IF, median serum stigmasterol levels increased over tenfold when compared to healthy control neonates while being over threefold higher among those who develop IFALD [9]. Stigmasterol levels correlated positively with biochemical markers of liver injury and remained elevated after weaning off PN in those neonates with ongoing IFALD based on deranged liver biochemistry. Although not proving causal relationship, these observations support proinflammatory and cholestatic effects of intravenous plant sterols also in humans.

In mice, enteral nutrient deprivation and PN were associated with intestinal *Proteobacteria* overgrowth, mucosal inflammation, and epithelial barrier dysfunction, resulting in bacterial translocation [41]. Clinical studies have provided evidence that SBS is associated with respective shift in intestinal microbiota and intestinal barrier dysfunction also in humans. Enteral deprivation and PN promote mucosal atrophy and loss of intestinal epithelial barrier function in healthy volunteers and in children following intestinal resection, while PN-dependent SBS patients were systematically exposed to LPS [22, 42–44]. Many other factors affecting intestinal function in IF patients are also important in this respect. After resection, abnormal dilatation of the remaining small bowel, deranged intestinal motility patterns, and frequent loss of the ICV predispose to profound disturbances within the intestinal microbiota [3]. In addition, PN lipid constituents such as plant sterols may even promote selection and overabundance of specific bacterial species, which associate with cholestasis in PN-infused mice with intestinal barrier dysfunction [45]. Modulation of intestinal microbiota by PN plant sterols could be mediated through inhibition of FXR, which participates in the regulation of intestinal bacterial overgrowth and maintenance of epithelial barrier function [46]. In accordance with experimental studies, clinical data indicate that PN-dependent children with IF have altered intestinal microbiota characterized by overabundance of *Proteobacteria* [32]. *Proteobacteria* are opportunistic Gram-negative pathogens, which produce LPS and normally form a very small proportion of intestinal microbiota. Their overabundance associated with histological liver steatosis, fibrosis, and portal inflammation and also with intestinal inflammation as measured by fecal matrix metalloproteinase excretion [32]. Taken together, profound alterations in intestinal microbiota and epithelial barrier dysfunction occur in patients with IF, and these changes have been shown to associate with histological liver injury.

In pediatric onset IF, histological liver fibrosis and steatosis persist after cessation of PN, supporting a central role of compromised intestinal function in the pathogenesis of IFALD [6]. Extensive small intestinal resection alone in pigs without PN causes histological liver fibrosis and steatosis together with increased hepatic expression of proinflammatory cytokines in association with altered intestinal microbiota, enhanced bacterial metabolization of bile acids, and FRX signaling [47]. In children with IF, partial or total loss of the distal small intestine (ileum) irrespective of PN delivery closely correlates with histological liver fibrosis along with decreased circulating fibroblast growth factor (FGF) 19 levels, which, in turn, was associated with portal inflammation and liver fibrosis. Ileal enterocytes secrete FGF 19 to portal circulation in response to FXR induction by absorbed bile acids [7]. In the liver, both FGF 19 and bile

acids returning from the intestine downregulate bile acid synthesis. Reclaimed bile acids inhibit bile acid synthesis through induction of FXR [48]. Ileal resection leads to diminished secretion of FGF 19 and decreased intestinal FXR transcription being confined to the ileum but also decreases FXR agonism in the liver due to interruption of enterohepatic circulation of bile acids after loss of their active ileal absorption site [49]. In mice, induction of intestinal FXR protects the liver from cholestatic injury by inducing FGF 15 (FGF 19 homologue in mice) expression and reducing hepatic accumulation of bile acids [50]. In addition to activation of hepatic bile acid synthesis, impaired FXR-FGF 19 axis has potential to promote liver injury in IF via multitude of mechanisms by interfering biliary bile acid and phospholipid secretion, inducing lipogenesis and inflammatory responses in the liver and by failing to prevent bacterial overgrowth and intestinal barrier dysfunction in the gut [46, 48, 51]. Reformed intestinal microbiota may mediate these effects by enhanced microbial transformation of bile acids altering their ability to active target receptors such as FXR and G protein-coupled member receptor TGR5. Of note, both FXR and TGR5 suppress hepatic fat accumulation [48, 52], which is associated with increased serum levels of FGF 21 in IF similar to patients with nonalcoholic fatty liver disease [16]. Altered intestinal microbiota may essentially promote liver injury also after weaning off PN and associated more strongly with liver steatosis than duration of PN or remaining bowel length in patients with pediatric onset IF [32]. Genetic susceptibility is likely to modify pathogenesis of IFALD, which would help to explain the large interindividual variation in the disease phenotype. Mutations of biliary phospholipid transporter gene *ABCB4* has been reported to correlate with PN-associated cholestasis in preterm infants [53]. Canalicular secretion of phospholipids protects cholangiocyte cell membranes from detergent action of bile acids and bile duct injury. Because *ABCB4* is also regulated by FXR, reduced phospholipid secretion may be also triggered by decreased FXR agonism in IF as featured above. This could be one underlying mechanism for the high incidence of cholelithiasis in patients with IF analogous to low phospholipid-associated cholelithiasis.

Conclusions

During the recent years, we have witnessed significant advancements in understanding the pathogenesis of IFALD. Despite this progression, incidence of neonatal IFALD has remained unchanged, although experienced individual centers have been able to limit the disease progression avoiding liver failure by multidisciplinary measures [29, 54]. Future studies are needed to unravel causal relationships between different etiological factors, which could allow development of prevention and treatment strategies based on critical disease mechanisms. These strategies should be tested in adequately powered multicenter randomized trials. Further clinical studies are also needed to evaluate the long-term consequences and the natural history of IFALD-associated histological liver injury following weaning off PN. At the same time, development of more accurate noninvasive diagnostic modalities to replace liver biopsy is required to serve in clinical patient surveillance and in performance of these clinical trials [55]. Recognition of the potential role of FXR signaling in the pathogenesis of IFALD provides theoretical basis for future treatment by utilizing synthetic FXR agonists such as obeticholic acid, which have already provided promising clinical results in various liver disorders in adults [56].

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Recent Advances in Nutritional Care of Patients with Intestinal Failure

5

Antonella Diamanti, Teresa Capriati, and Domenica Elia

Abbreviations

ASPEN	American Society for Parenteral and Enteral Nutrition
AFs	Amino acid-based formulas
BF	Breastfeeding
CIPOs	Chronic intestinal pseudo-obstructions
CVC	Central venous catheter
EN	Enteral nutrition
FO	Fish oil-based LEs
HD	Hirschsprung's diseases
HFs	Hydrolyzed formulas
HPN	Home parenteral nutrition
IF	Intestinal failure
IFALD	Intestinal failure-associated liver disease
ITx	Intestinal transplant
LCTs	Long-chain triglycerides
LEs	Lipid emulsions
MCTs	Medium-chain triglycerides
PN	Parenteral nutrition
PUFA	Polyunsaturated fatty acids
SBS	Short bowel syndrome
SCFAs	Short-chain fatty acids
SMOF lipids	Mixture of 30 % of SO, 30 % of coconut oil, 25 % of olive oil, and 15 % of FO
SO	Soybean oil-based lipids

A. Diamanti, MD (✉)
Hepatology, Gastroenterology and Nutrition Unit, Bambino Gesù "Children Hospital", Piazza S. Onofrio 4, Rome 00165, Italy
e-mail: antonella.diamanti@opbg.net

T. Capriati • D. Elia
Artificial Nutrition Unit, Bambino Gesù Children's Hospital, P.zza S Onofrio 4, Rome 00165, Italy

Introduction

Intestinal failure (IF) refers to all states where the intestine has inadequate absorptive capacity to meet nutritional, fluid, and electrolyte needs to sustain life and growth requirements of a child [1]. IF leads to chronic dependence on parenteral nutrition (PN) to maintain adequate growth, hydration, and micronutrient balance. PN requirements remain the best measure of the degree of IF [1, 2]. Severe liver disease, recurrent catheter sepsis, and loss of venous access can determine failure to provide long-term nourishment to an IF child dependent on PN, and that condition identifies the so-called nutritional failure [3]. According to the current long-term graft's and patient's survival following intestinal transplant (ITx), IF is considered as a controversial indication to ITx while nutritional failure as an accepted indication to that [3, 4].

The etiology of IF recognizes the short bowel syndrome (SBS) where congenital or acquired lesions have determined extensive loss of intestinal mass, as the most frequent underlying IF

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disease [2]. Malabsorption due to ineffective mucosal surface (congenital enterocyte disorders, including microvillus inclusion disease, tufting enteropathy, phenotypic diarrhea, and autoimmune enteropathy) and motility disorders with undamaged mucosal surface but wide motility dysfunctions (chronic intestinal pseudo-obstructions, CIPOs; gastroschisis not associated with small bowel resection and Hirschsprung's diseases (HD) are further categories of IF [1–3, 5]. Some neurological diseases which on the long-term acquire progressively intestinal dysfunction with gut dysmotility, such as severe cerebral palsy, are emerging causes of IF [5].

The key concept of the overall nutritional care is to integrate the maximum tolerated amount of enteral intake with the ongoing support of PN [6]. The final objective is to achieve total or partial intestinal rehabilitation that can be fast or quite prolonged, depending on the type of injury, but that is possible even in children with congenital enterocyte disorders [7].

Nutritional Care of IF

The nutritional care of pediatric IF can be summarized as follows: (1) early managing of fluid and electrolyte losses before starting PN and enteral nutrition (EN); (2) providing adequate PN, for growth and normal development; (3) promoting intestinal rehabilitation by optimizing EN; (4) discharging on home parenteral nutrition (HPN) the patients with predicted long-term PN; and (5) preventing/treating complications related to the patient's underlying disease and their PN.

Early Managing of Fluid and Electrolyte Losses

All clinical forms of IF require a complex preliminary phase of fluid and electrolyte management, before beginning the appropriate nutritional program. SBS patients, at the early stages after bowel resection, have increased losses of fluids and electrolytes which can lead to significant electrolyte imbalance and dehydration. Early restoration of fluid and electrolyte homeostasis is therefore required, and it needs aggressive recovery with fluids [6]. Similarly, in newborns with congenital enteropathies, especially in microvillus diseases, severe watery diarrhea develops in the first few days after birth that does not stop during fasting, and it may cause life-threatening electrolyte and acid-base imbalances, rapid and severe dehydration, and hypovolemic shock [3]. Congenital forms of CIPOs present shortly after birth with episodes of intestinal obstruction [3]; major fluid/electrolyte imbalances related to proximal gastrointestinal stomas or fistula, extreme bowel dilatation with bacterial overgrowth and intractable abdominal pain, and careful clinical management require also in such type of IF careful replacement strategies [1].

Therefore, fluid restoration is crucial in this phase; fluid replacement is determined by the volume of overall digestive losses, and if it is not appropriate, dehydration and electrolyte abnormalities may occur [1]. Early fluid replacement is usually 1 mL for every mL of fluid loss.

This phase is followed by PN beginning. Timing of PN initiation will depend on the underlying disease, background nutritional status, and the age of the child. Previously, well-nourished children should start PN supports if they will be unable to achieve enteral autonomy by 5–7 days. Overall, undernourished patients or with neonatal onset IF who have low tissue reserves and therefore increased nutritional risk duration is shorter for, require earlier PN beginning [8].

Providing Adequate PN

Before approaching each PN program, a reliable vascular access should be warranted. The choice of the access is dependent on the predicted length of the PN support. Peripherally inserted central lines are very effective means of providing PN over a short to medium term, while more definitive central venous access are required for prolonged PN. Ultrasound-guided venipuncture (by real-time ultrasonography) is associated with lower incidence of complications and higher rate of success than "blind" venipuncture. Ultrasound support is

therefore strongly recommended for all CVC insertions, and it is increasingly employed [9]. Placement by surgical cutdown is not recommended, in terms of cost-effectiveness and risk of infection [10].

The expertise of a dedicated hospital-based nutritional team is required to tailor PN to the single patient and to manage central catheters; it is supported by official guidelines published by the pertinent societies [8, 10].

IF patients are at risk for developing intestinal failure-associated liver disease (IFALD) [11] due to IF-related factors, such as lack of enteral feeding, disturbed enterohepatic bile flow, presence of inflammation, oxidative stress, immaturity of the liver, and infections, but also PN-related factors [11]. Therefore, in patients who are predicted to require long-term treatments, PN should be adapted to reduce the risk of liver injury [3, 12]. A further chapter widely treats IFALD; however, for our purpose, two aspects of the PN management deserve specific consideration:

A. Choosing lipid emulsions (LEs)
B. Optimizing non-lipid intake

Choosing LEs

Historically, a French study delineated that IFALD in adult HPN patients has a value of at least 1.5-fold the upper limit of normal on 2 of 3 liver function measures for cholestasis that persists for more than 6 months [13]. This study also showed that chronic cholestasis predicts serious liver problems and is associated with the use of soybean oil-based lipids (SO) at doses >1 g/kg/day [13]. Several factors may explicate how LEs can impact on the development of IFALD:

(a) Activation of hepatic macrophages (Kupffer cells) by excess ω-6 polyunsaturated fatty acids (PUFA) in SO that leads to the production of proinflammatory cytokines derived from linoleic and arachidonic acids [14].
(b) High intake of phytosterols (e.g., stigmasterol and campesterol, equivalents of cholesterol in vegetable oils) derived from SO; they have structural similarity to bile acids and may act as antagonists to nuclear bile receptors that are protective against cholestasis [14].
(c) Overall content of vitamin E, especially of its most bioactive isoform α-tocopherol, which protects PUFAs from oxidative damage due to lipid peroxidation. The addition of this component to SO has been shown to reduce liver damage in a piglet model of IFALD [14].

Published surveys report that the use of a fish oil-based LEs (FO) is able to reverse IFALD [15, 16]. These surveys, nevertheless, are used at a markedly decreased dosage of FO (1 g/kg/d) if compared to that of SO in the control historic group (3 g/kg/day) [15]. That supports the hypothesis that the overall decreased fat intake rather than FO supplementation is important in reversing IFALD [14]. Interestingly, a recently published paper reports two cases of reverted cholestasis by switching from SMOF lipid (Fresenius Kabi, Bad Homburg, Germany), an emulsion containing a mixture of 30 % of SO, 30 % of coconut oil, 25 % of olive oil, and 15 % of FO at 2.0–3.0 g/kg/day, to FO at 1 g/kg/day [17]. That supports the hypothesis that the reduced amount rather than the type of LEs may be hepatotoxic.

Anyway, FO monotherapy is now widely employed in clinical practice. FO alone may not be able to provide enough energy to sustain growth. A mixed LE containing soybean oil (SMOF lipid) compared with SO in a blinded randomized controlled trial in pediatric HPN patients resulted in mild changes in total bilirubin when administered 4–5 times per week at 2 g/kg/day and in normal growth pattern [18].

In North America, FO alone (Omegaven, Fresenius Kabi, Bad Homburg, Germany) is available on the market, whereas in Europe, it is possible to use LEs containing the mixture (SMOF lipid, Fresenius Kabi, Bad Homburg, Germany). That led to develop two different approaches to optimize LEs used in the United States and Canada as compared with Europe.

Many institutions generally combine the use of novel lipid preparations and reduced rates of administration of SO to prevent the development

Table 5.1 Composition of lipid emulsions available for parenteral nutrition

Emulsion (% fat) (Manufacturer)	Lipid source (%)	ω6:ω3 ratio	Phytosterols (mg/L)	α-Tocopherol (μmol/L)
Intralipid 20% (Fresenius Kabi)	SO 100%	7:1	348 ± 33	87
Lipofundin 20% (BBraun)	SO 50% MCT 50%	7:1	No data	502
ClinOleic-Clinolipid 20% (Baxter)	SO 20% OO 100%	9:1	327 ± 8	75
Lipoplus 20% (BBRaun)	SO 40% MCT 50% FO 10%	2.7:1	No data	562
SMOF lipid 20% (Fresenius)	SO 30% MCT 30% OO 25% FO 15%	2.5:1	47.6	500
Omegaven 10% (Fresenius)	FO 100%	1:8	0	505

SO Soybean, *MCT* Medium-chain triglycerides, *OO* olive oil, *FO* fish oil

of liver disease [14]; e.g., if bilirubin exceeds 34 μg/L, lipid intake is reduced at 1 g/k/day, while if it goes over 50 μg/L, the lipid source is changed to FO alone at 1 g/kg/day.

Table 5.1 summarizes the composition of available LEs employed in PN.

Optimization of Non-lipid Intake

Excessive glucose intake causes increased lipogenesis and fat tissue deposition together with subsequent liver steatosis and enhanced production of triglycerides by the liver [8]. The American Society for Parenteral and Enteral Nutrition (ASPEN) [19]; the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition [11]; and the American Academy of Pediatrics guidelines [20] recommend limiting the glucose infusion rate (GIR) at 12–14 mg/kg/min (18 g/kg per day) in infants and young children up to 2 years. Glucose intake should usually cover 60–75% of nonprotein calories [8]. As above reported, reduced LE intake as strategy to prevent/treat IFALD may be required; in such cases, increased glucose intake, to better satisfy the nutritional needs, resulted well tolerated [21].

Furthermore, prophylactic cycling of PN may reduce the incidence of IFALD [14]. Cyclical PN is well tolerated and may be 3–6 months of age. In cyclical PN, the maximal rate of glucose infusion may exceed the advised GIR. The maximal infusion rate should not exceed 1.2 g/kg per hour (20 mg/kg per min). A stepwise increase and decrease of glucose infusion rate at onset and at discontinuation of the infusion should be considered to avoid hyper- and hypoglycemia, respectively. A reliable method for tapering is to halve the rate for 30 min and then to halve this again for an additional 30 min. Glucose tolerance should be monitored during the first phases of the cycling PN [8].

With regard to the choice of amino acid solution, there is evidence that supplementation of TrophAmine may reduce the incidence of IFALD in certain high-risk populations such as those with NEC [12].

Furthermore, copper and manganese serum levels from PN solutions should be monitored closely in patients who have developed IFALD because they may exacerbate it [12].

Promoting EN

The provision of enteral nutrients is a critical component of the therapy of IF; in SBS patients, it represents the fundamental driver of adaptation [12]. Early attempts of oral nutrition confer the critical window of opportunity for establishing normal suck and swallow patterns; if this is not attended, the child is at risk for oral aversion, which has many long-term negative consequences [22]. The most pragmatic way to address EN handling in IF should take into account that all patients regardless the etiology of their IF may

recover to a variable degree and that the strategies to promote EN should be reconsidered on a day-to-day basis. The overall care of IF is based on the judicious integration of two overlapped goals: progressive advancement of enteral calories and gradual weaning from the ongoing support of PN, maintaining a weight gain [6]. If tube feeding is used, the practice of inserting a gastrostomy early allows a more controlled method of delivering feed with an opportunity to preserve and promote voluntary feeding without the negative effects of the long-term presence of a nasal tube [22]. If patients with motility disorders but also with SBS show poor tolerance to gastric feeding, the post-pyloric EN approach should be tried [23]. The main aspects concerning the EN management in IF are:

Choosing the formula
Assessing methods of feeding
Assessing tolerance to EN
Using enteral supplements
Starting and handling complementary foods

Choosing the Formula

There is a paucity of evidence in favoring one type of feed over the other in this setting; however, breastfeeding (BF) should be used when tolerated as it helps and promotes adaptation [24]. The full advantages of BF include the optimal macronutrient composition for human infant growth, with a full complement of macro- and micronutrients [25, 26]. In addition, it contains trophic factors such as epidermal growth factor, which likely augment the adaptive process [1]. Furthermore, BF contains immunoglobulins and natural antimicrobial properties which both enhance mucosal barrier function and prevent dangerous overgrowth of bacteria within intestinal lumen. Finally, it promotes intestinal colonization by appropriate lactobacilli and related bacteria which are important elements of healthy microbiome [27, 28]. Bovine colostrum also seems to confer beneficial effects on IF [29].

Finally, BF supports physiological and psychological between infant and mother. If the mother's own milk is not available, banked breast milk even with pasteurization has nearly identical physiologic benefits [25]. Overall, BF should be the first choice in all IF patients.

If BF is not available, formula selection should be based on (a) low allergenicity especially in SBS infants who are at high risk for allergy [30]; (b) fat profile based on a combination of medium-chain triglycerides (MCTs) and long-chain triglycerides (LCTs) (ratio of MCTs to LCTs of 30/70 %) that seems to favor fat absorption in patients with significant intestinal resection, with or without colon in continuity [31]; (c) pre-hydrolyzed protein content that may be more suitable than whole proteins to give nitrogen source to an inefficient mucosal surface [26]; (d) low osmolality (less than 310 mOsM/L) to minimize the risk for osmotic diarrhea [32, 33]; and (e) glucose polymer as main carbohydrate source rather than lactose, due to the possible lactose intolerance, especially in SBS children [9].

Some extensively hydrolyzed formulas (HFs) and amino acid-based formulas (AFs) meet the above reported criteria. AFs have been shown effective in decreasing PN length in small and not controlled series of SBS patients [11, 34].

In adults, polymeric formulas are better tolerated than HFs and AAs; thus we can deduce that in non-neonatal forms of IF such as in IF acquired in childhood and adolescence, the use of polymeric formulas may be appropriate [35, 36].

Table 5.2 shows the criteria for choosing the best formula when the BF is not available.

Table 5.2 Criteria for choosing the best formula when breastfeeding is not available

Criteria for choosing	Best formula	References
Allergenicity	AAs > HFs > polymeric formulas	[30]
Fat profile as MCTs/LCTs	HFs > AAs > polymeric formulas	[31]
More absorbable nitrogen source	HFs > AAs > polymeric formulas	[26]
Osmolality	HFs > AAs > polymeric formulas	[32, 33]
Glucose polymer as main CH source	Polymeric formulas and HFs > AAs	[9]

MCT medium-chain triglycerides, *LCTs* long-chain triglycerides, *CH* carbohydrates, *AAs* amino acid-based formulas, *HFs* hydrolyzed-based formulas

Methods of Feeding

EN should be started as soon as postoperative ileus resolves [9, 37], by the most physiological mode. This ideally should be in the form of oral bolus feeding via breast or bottle. In infants unable to tolerate oral feeds, nasogastric tube feeding is needed. Continuous tube feeding is associated with increased feed tolerance by improved mucosal contact and decreased transit time within the gut [9]. Bolus tube feeding helps gut motility and adaptation and provides periods of fasting, thus reducing persistent hyperinsulinemia. After establishing an appropriate base of enteral nutrients, the general pattern is to increase the provision of enteral nutrients by a slow but steady increment, beginning at 10–20 mL/kg/day (for the average newborn). After the infant can tolerate continuous feeds of 5 mL/h, it is extremely useful to begin transition to oral feeds, providing in small quantities, 3–4 bolus oral feedings a day (equal or less than the volume continuously tolerated per hour). After establishing a stable feeding pattern, feeds are steadily increased on a daily basis [9]. In order to maximize overall enteral intake, it is often helpful to have continuous drips overnight. To correctly switch from PN to EN, it needs to consider that the net caloric extraction from EN is not 100 % as from PN and that macronutrient absorption from EN is superior than that of electrolytes and fluids. Therefore, PN should be decreased according to the calories provided by EN and not volume for volume [35, 36].

Assessing Tolerance to EN

Tolerance to enteral feeds is based on several factors and is dependent on IF etiology. In SBS infants, increasing stool output, vomiting, and irritability may suggest poor tolerance to EN regimen. If stool output is between 30 and 40 mL/kg body weight, EN needs to be carefully increased. Doubled stool output and output >40 mL/kg/day are contraindications to increase enteral feeds and indications to deal with a short-term reduction in feeding volume that will be gradually reintroduced. Stool frequency greater than six times per day should induce to cautiously increase EN [9].

Congenital enteropathies, in particular the microvillus inclusion disease, are responsible for severe and profuse diarrhea (up to 150–200 mL/kg/day) beginning at birth [9] and persistent at bowel rest. In a case series including seven patients with tufting enteropathies, after a period of exclusive PN ranging from 42 to 105 days, oral or enteral feeding was reintroduced progressively in all of the patients [38]. In this IF category, the high output makes difficult to judge the tolerance to EN. We can suggest that, according to that reported in SBS, the doubled output may be a contraindication to increase EN.

IF infants with motility disorders recurrent of symptoms suggestive for occlusion (vomiting, abdominal distension, constipation) may suggest intolerance to EN. Stoma output greater than 20 ml/kg/day may be a red flag of intolerance as in SBS infants.

Carbohydrate intolerance that determines frequent and liquid stools is frequent in IF patients, and it can be suggested by the presence of reducing substances on the stools and by the stool pH <6.

The rise in plasma citrulline concentration frequently accompanies the successful achieving of enteral tolerance. Citrulline is a nonessential amino acid produced by the enterocytes of the small bowel; its serum level has been shown to reflect intestinal mass in various gastrointestinal diseases. Citrulline concentration of 12–15 μmol/L or greater following EN beginning seems to predict a successful PN withdrawal [35, 36].

Several categories of drugs can help in optimizing EN tolerance [35]. Antidiarrheal drugs (like loperamide and codeine phosphate) help by increasing contact time with mucosal lining and hence increasing absorption. Proton pump inhibitors can help control this gastric hypersecretion and reduce stool output. Antisecretory drugs, e.g., octreotide and clonidine, have some role in high-output diarrhea in SBS. Rotating cycles of antibiotics may be helpful in reducing small bowel bacterial overgrowth (SBBO) suggested by abdominal distension, watery diarrhea, and dysmotility.

The pharmacologic approach to IF will be specifically treated in another chapter of this volume.

We summarize in Fig. 5.1 the management of EN in IF at neonatal onset and in Table 5.3 the diagnostic tools useful to assess tolerance to EN and optimize EN intake.

Use of Enteral Supplements

IF patients can lose bicarbonate and sodium in their stool or stoma, which must be closely monitored and replaced, not only intravenously but also via enteral route [5]. It is important to monitor sodium balance, because sodium deficiency can limit growth in infants [1, 35]. The simple spot measurement of the urinary sodium and, in selected cases, the calculation of the fractional excretion of sodium are rapid and efficient ways to monitor the sodium loss. If the spot urine sodium is <10 mEq/L, increased sodium intake, both in EN and in PN, is required. The sodium content in PN should be titrated to keep urine sodium >30 mEq/L and to maintain urine sodium

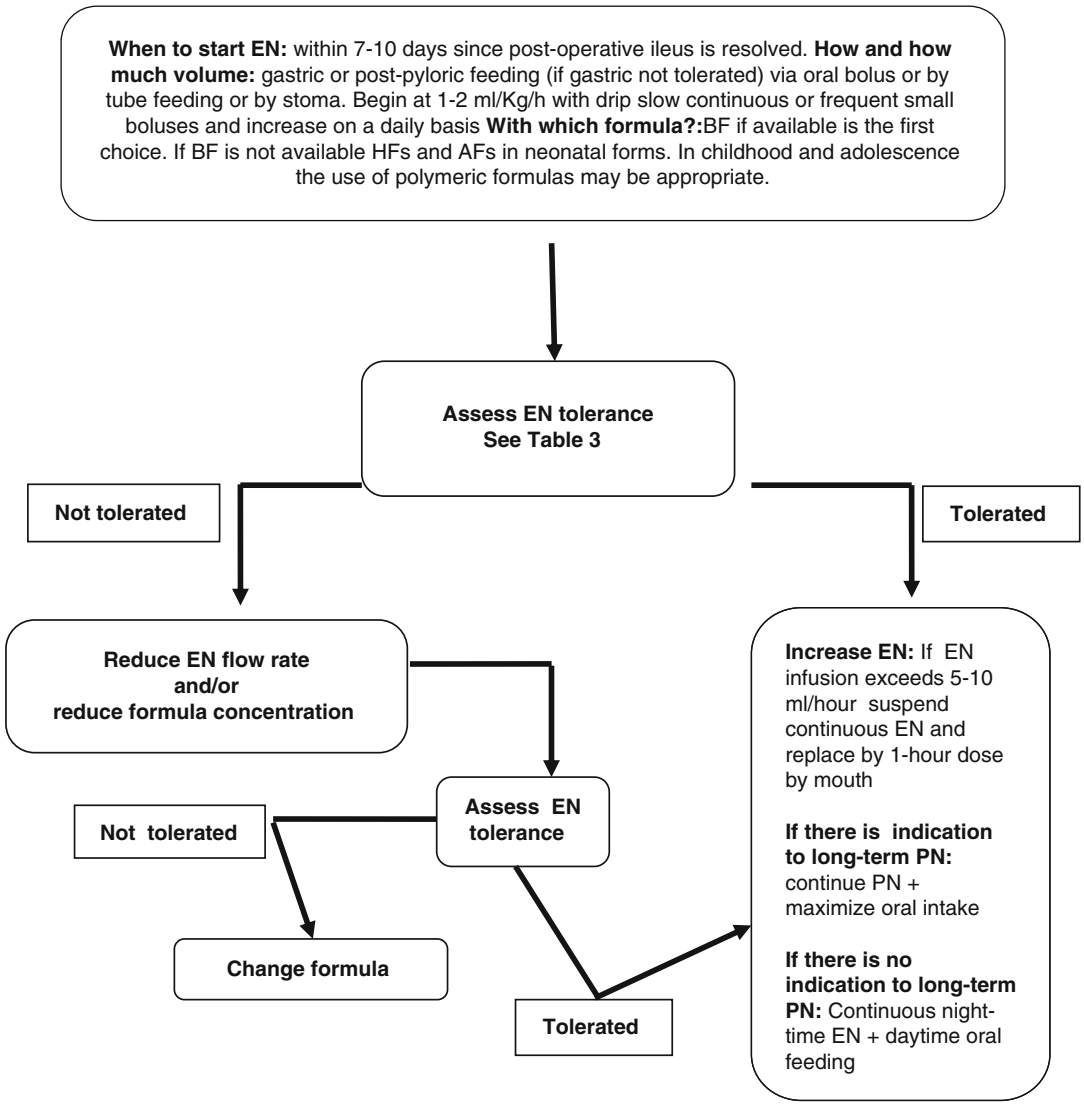


Fig. 5.1 Management of enteral nutrition in intestinal failure. *EN* enteral nutrition, *BF* breastfeeding, *HFs* hydrolyzed formulas, *AAs* amino acid-based formulas, *PN* parenteral nutrition

Table 5.3 Diagnostic tools to assess tolerance to EN and optimize EN intake

	Assessment of tolerance to EN	References
Clinical markers	1. Weight and stool pattern (diaper that contains only urine several times/day; less than 6–8 stools/day; absence of diaper rash due to liquid feces; lack of weight gain)	[9, 35, 37]
	2. Amount of stool output (between 30 and 40 ml/kg body weight; higher than > 50 % respect basal output or loss from ostomy about 50 ml/Kg/day)	
	3. Symptoms suggestive for occlusion (vomiting, abdominal distension, constipation) in patients with motility disorders	
Biochemical markers	1. Plasma citrulline concentration (in SBS patients, levels > 12–15 μmol/L indicate adaptation)	[1, 3, 35, 36]
	2. pH of feces (values < 5 indicates acid and not absorbed stools)	
	3. Urine electrolytes (sodium > 30 mEq/L and urine sodium to potassium ratio at least 1:1 indicate good hydration)	

to potassium ratio at least 1:1. Weekly monitoring of the urinary sodium is a preemptive way of assessing status, rather than waiting for the serum level to drop, and long-term monitoring of this parameter is suggested [1].

When increasing in feeds does not result in appropriate weight gain, it should consider supplementation with additional fat [6]. There is good rationale for using long-chain fats (LCTs) as supplemental vegetable oils, or olive oil, or emulsified preparations. Additionally, it may be reasonable to add MCTs because they are absorbed directly across the enterocyte membrane, without requiring lymphatic absorption. This occurs in the proximal small bowel and even the stomach; therefore, adding gradually increasing amounts of MCTs to the formula being used, especially if delivered by tube feeds, may favorably increase the overall caloric intake. MCTs are nevertheless less effective than LCTs in promoting intestinal adaptation [38].

Starting and Handling Complementary Foods

The introduction of complementary, age-appropriate foods between 4 and 6 months of age, as well as oral boluses of human milk/formula as soon as tolerated, is helpful to stimulate oral-motor development and to prevent feeding aversion [5].

Early weaning (17 weeks) has the advantage of promoting feeding maturation with respect to solids and a reduction in milk fluid volume which may exacerbate a tendency to vomit or induce an increase in osmotically driven stomal losses [5]. Feeding therapy is usually required as these infants are likely to have some degree of oral aversion due to delayed introduction of oral feeds as a result of prematurity, prolonged intubation, and cardiovascular instability.

Patients without a colon tolerate better diets that are high in fat (30–40 % of caloric intake), whereas those with intact colons experience steatorrhea, magnesium, and calcium loss with high-fat intake. With calcium loss, oxalate absorption is enhanced in the colon and kidneys, which can lead to the formation of oxalate renal stones [39, 40]. Hence, it is necessary to restrict oxalate intake in SBS patients with a colon to decrease the risk of oxalate renal stones. Oral calcium supplements can also reduce the formation of oxalate stones.

Soluble dietary fiber (pectin or guar gum) can slow gastrointestinal transit time allowing for improved absorption (see above). The soluble fiber in the colon is fermented to short-chain fatty acids, including butyrate which is an energy source for colonocytes. In addition, the butyrate regulates colonocyte proliferation and improves water and sodium absorption by upregulating the

sodium-hydrogen exchangers [1]. However, excess pectin (>3 %) can lead to an osmotic diarrhea which can counteract its benefits.

In children with short bowel, there is a potential for significant malabsorption of carbohydrates especially lactose. Therefore, feed with a glucose polymer as a main carbohydrate source is likely to be better tolerated [9]. Solids rich in complex carbohydrates, such as cereals and soluble fibers, lean meat, and unsweetened fruits, are well tolerated in patients with little or intact colon. Patients without colon or with stoma tolerate foods at high lipid contents and poor carbohydrates.

Some forms of IF at neonatal onset, in particular in SBS, may be useful to test the tolerance to cow's milk proteins when complementary feeding is started. In Fig. 5.2, we present a practical algorithm that can be useful for this purpose.

Discharging on HPN

HPN represents the best care option in infants who do not need hospitalization but are dependent on long-term PN. It is indicated in irreversible IF or when the transition from PN to full EN is possible over a short period [41]. Patients eligible for HPN should be clinically stable. As soon as sufficient stability is reached, the child should be discharged under continued outpatient care with a team experienced in intestinal rehabilitation. A coordinated multidisciplinary approach is essential throughout, and the early training of parents in the complexity of HPN care is essential. A specialized nurse dedicated to the coordination of the HPN service is essential, and once the funding and provision of a HPN service is put in place, early discharge home benefits the child and family [5]. Transferring care of these children from hospital to home has a positive influence on CVC infections, social circumstances, as well as reducing the cost of treatment. At the same time, it also puts a significant burden on the family who has to spend a lot of time caring for the child and have difficulty in maintaining gainful employment [41].

Preventing/Treating Complications

The complications of IF [42–50] can be subdivided into two main categories:

A. CVC-related complications
B. IF-/PN-related complications

Main complications and suggested way of prevention are summarized in Fig. 5.3.

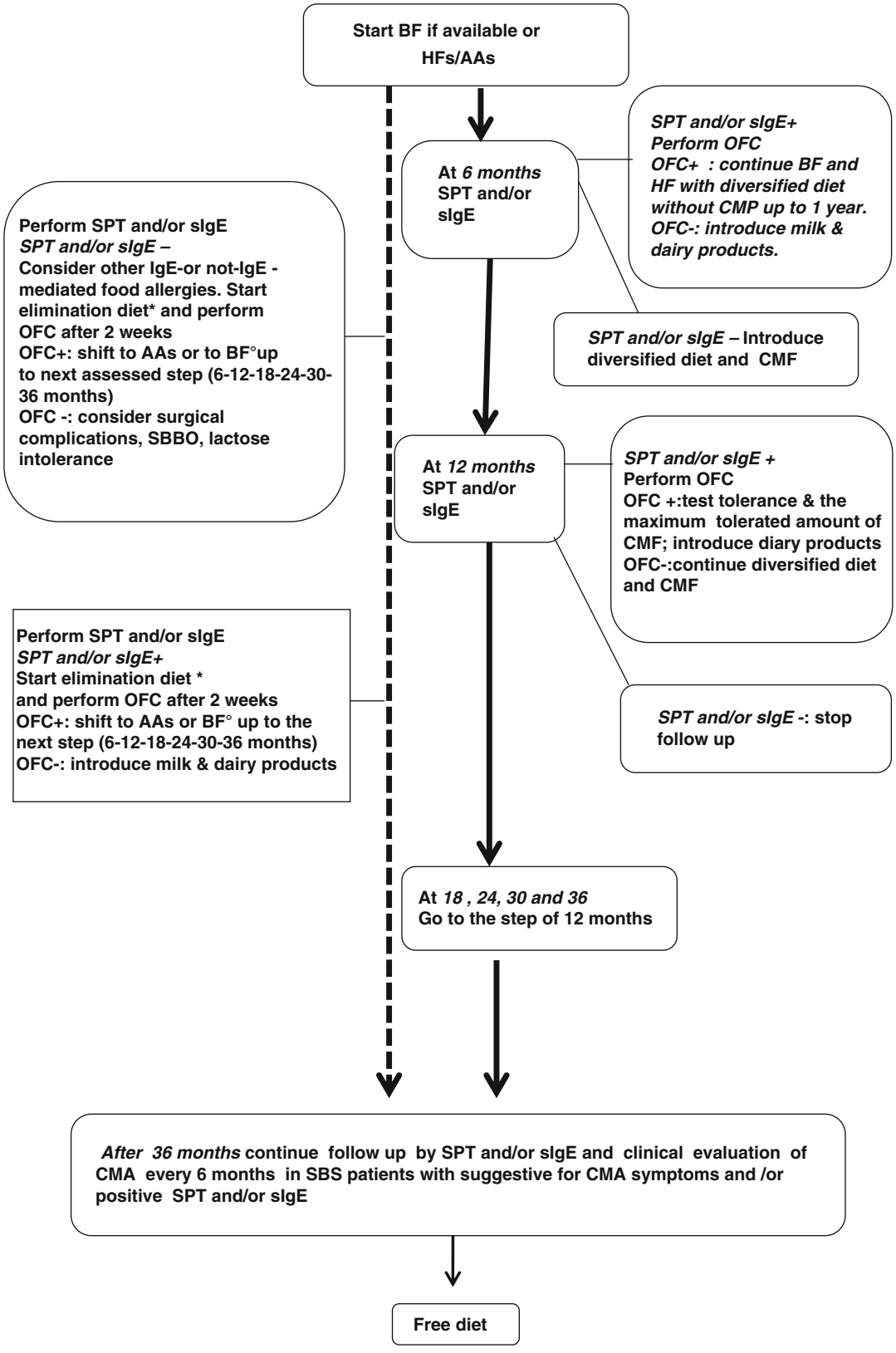
CVC-Related Complications

Administration of long-term PN requires placement of indwelling central venous catheter. The problems associated with central lines include infections, mechanical damage, blockages, and thrombosis. Infections are the commonest complication with incidence being around 1–6 per 1000 days of PN [9]. Prevention of infections is based on optimal catheter placement and strict hand hygiene. Taurolidine, a derivative of amino acid taurine, has been shown to have a role in reducing catheter-related sepsis [51]. With advances in the type of catheters used and insertion techniques, there has been a significant reduction in complications [10].

IF-/PN-Related Complications

Trace element depletion is very common among patients with surgical short bowel syndrome if parenteral administration is inadequate. Adequate parenteral zinc supplementation is particularly important; its deficiency is generally associated with high output from stoma but also with congenital diarrhea. As zinc is a cofactor for alkaline phosphatase synthesis, an excellent surrogate marker for zinc deficiency is the serum alkaline phosphatase level, which is likely decreased in patients at risk for the clinical manifestations of zinc deficiency [1].

D-lactic acidosis occurs among patients whose gastrointestinal tract is colonized by d-lactate-synthesizing organisms. Humans have the ability


Start BF if available or HFs/AAs
At 6 months SPT and/or sIgE
SPT and/or sIgE+ Perform OFC OFC+ : continue BF and HF with diversified diet without CMP up to 1 year. OFC-: introduce milk & dairy products.
SPT and/or sIgE – Introduce diversified diet and CMF
Perform SPT and/or sIgE SPT and/or sIgE – Consider other IgE-or not-IgE - mediated food allergies. Start elimination diet* and perform OFC after 2 weeks OFC+: shift to AAs or to BF°up to next assessed step (6-12-18-24-30-36 months) OFC -: consider surgical complications, SBBO, lactose intolerance
At 12 months SPT and/or sIgE
SPT and/or sIgE + Perform OFC OFC +:test tolerance & the maximum tolerated amount of CMF; introduce diary products OFC-:continue diversified diet and CMF
Perform SPT and/or sIgE SPT and/or sIgE+ Start elimination diet * and perform OFC after 2 weeks OFC+: shift to AAs or BF° up to the next step (6-12-18-24-30-36 months) OFC-: introduce milk & dairy products
SPT and/or sIgE -: stop follow up
At 18 , 24, 30 and 36 Go to the step of 12 months
After 36 months continue follow up by SPT and/or sIgE and clinical evaluation of CMA every 6 months in SBS patients with suggestive for CMA symptoms and /or positive SPT and/or sIgE
Free diet

to rapidly catabolize L-lactate, which is a product of human anaerobic metabolism, but d-lactate can be catabolized and cleared very slowly, and toxic blood levels can build up when the small intestine is overgrown with anaerobic bacteria. Signs and symptoms of d-lactic acidosis include confusion, somnolence, dementia, ataxia, or even seizures. This condition is characterized by acidosis associated with an anion gap but a normal blood L-lactate level. Lactobacilli and other bacteria, including *Clostridium perfringens* and *Streptococcus bovis*, when present, may ferment nonabsorbed carbohydrate to D-lactic acid, which cannot be metabolized by L-lactate dehydrogenase [38]. These microorganisms may proliferate in the acidic environment of the colon that is the result of the metabolism of unabsorbed carbohydrate to short-chain fatty acids (SCFAs). D-lactic acidosis presents with encephalopathy (ataxia, blurred speech, decreased consciousness) and should be considered when there is a high anion gap metabolic acidosis with normal serum lactate and high gram + strains in the stools [35]. Preventive measures for D-lactic acidosis include the reduction of carbohydrate intake, followed by antibiotics (such as metronidazole or cotrimoxazole) when dietary changes fail [47].

Vitamin B12 absorption may be impaired among patients who have undergone distal small bowel resections. Serum levels of B12 are sometimes falsely elevated because of the production of biologically inactive B12 analogues among patients with bacterial overgrowth syndrome [39].

Provision of enteral water-soluble vitamins is unnecessary while patients are on parenteral vitamin supplements, but if adaptation occurs and patients are weaned off PN, enteral provision of most water-soluble vitamins is advisable. Fat-soluble vitamin supplementation is delivered via parenteral vitamins and parenteral lipid generally preventing deficiency, but after weaning off PN, enteral supplementation is advisable.

Iron deficiency can occur in patients with SBS, but it is frequently correctable with oral iron supplements because the efficiency of enteral iron absorption is maximal in the duodenum which is often maintained after neonatal surgical resections. For patients who cannot tolerate enteral iron or who remain deficient despite enteral supplementation, parenteral iron may be given. Iron deficiency can be also due to chronic gastrointestinal bleeding [35].

Another concern of the long-term PN is the potential exposure to toxic plasma aluminum concentrations. A recent Canadian survey found that in pediatric patients receiving long-term PN, aluminum intake is significantly greater than recommended by the US Food and Drug Administration to prevent aluminum toxicity. In IF patients on PN, aluminum is stored in the body because the protective gastrointestinal barrier is bypassed and renal function may be impaired. The long-term aluminum exposure can contribute to chronic bone disease (by inhibition of PTH) and to neurotoxicity of PN. In addition, it is involved in IFALD (it accumulates in the liver) and in the development of hypochromic, microcytic anemia (binding to transferrin).

Colonic oxalate absorption is increased in patients with SBS, resulting in hyperoxaluria and in calcium oxalate nephrolithiasis. The risk of stone formation is reduced if colon is partially or fully removed. Renal function can also be compromised by some antibiotics or by not corrected control of fluids and electrolytes in the first phase of IF.

Growth is usually impaired in IF at neonatal onset. These infants will be small, and to push their weight gain to the 50th percentile or higher is not physiologic. It is more appropriate to

Fig. 5.2 Practical algorithm for the evaluation of tolerance to cow's milk proteins. The *dotted arrow* represents the subjects who develop the symptoms between the steps. The *complete arrow* represents the subjects who don't show any symptoms between the steps. *SPT* skin prick tests, *CMA* cow's milk allergy, *BF* breastfeeding, *HFs* hydrolyzed formulas, *OFC* oral food challenge, *AAs* amino acid-based formulas, *CMP* cow's milk protein, *CMF* cow's milk-based formulas, *SBBO* small bowel bacterial overgrowth. *Elimination diet: AA in subjects receiving HF and maternal elimination of CMP in those receiving breastfeeding. BF°: maternal elimination of CMP, integrated by calcium

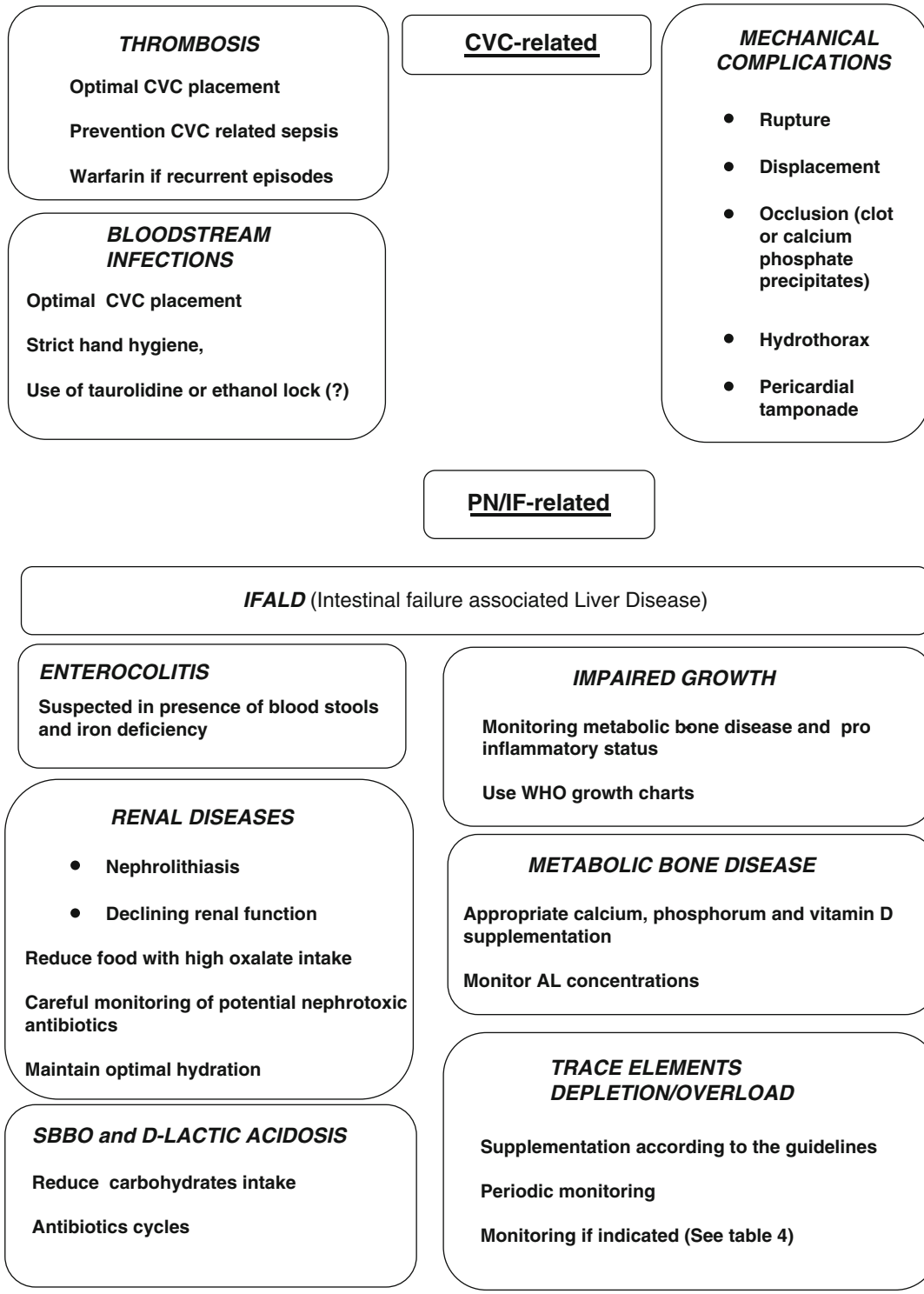


Fig. 5.3 Summary of parenteral nutrition complications. *CVC* central venous catheter, *PN* parenteral nutrition, *IF* intestinal failure, *IFALD* intestinal failure-associated liver disease, *WHO* World Health Organization, *SBBO* small bowel bacterial overgrowth

examine the birth record and weight and to use these to guide the decision as to which percentile seems appropriate. There should be careful serial measures of length, head, and weight gain, with plotting of the appropriate normative or "Z" scores. It may be necessary to tolerate a modest growth in weight, so long as growth in height and especially head circumference are maintained. It is likely appropriate to follow the WHO growth curves.

In Tables 5.4 and 5.5, we propose a plan of scheduled diagnostic tools to apply in the follow-up of IF patients.

Table 5.4 Plan of clinical and biochemical monitoring of intestinal failure

Timing	Clinical assessment[a]	Biochemical investigations
At PN beginning	Complete	PN profile[b], blood cell count, urine electrolytes, clotting test, urine-specific gravity
With every change in PN	Complete	PN profile, blood cell count, urine electrolytes
Weekly until stable	Complete	PN profile, blood cell count, urine electrolytes, urine-specific gravity
Each 1–3 months	Complete	PN profile blood cell count, urine electrolytes, clotting test, iron, total iron-binding capacity, ferritin, zinc, thyroid function tests
Each 6 months–1 year	Complete	Plasma vitamins A, E, and D. Red blood cell folate Plasma citrulline Tests for food allergies Blood in the stool
Each year	Complete	α-Fetoprotein
If indicated	*Ceruloplasmin and copper*: cholestasis, persistent anemia	
	Selenium: chronic diarrhea, high ostomy output (low alkaline phosphatase suggests low zinc levels)	
	Chromium: difficult glycemic control	
	D-lactate: encephalopathy, anion gap metabolic acidosis	
	Manganese: cholestasis	
	Serum B12: ileal resection, macrocytic anemia	
	Blood cultures: suspected CRBSI	
	Stool cultures: suspected SBBO and D-Lactic acidosis	

[a]Clinical evaluation (weight, height, clinical examination, and dietetic assessment)
[b]*PN profile* parenteral nutrition profile (renal and liver panel, calcium, phosphate, magnesium, electrolytes, total protein, serum albumin, triglycerides, bile acids, prealbumin, glucose level)

Table 5.5 Plan of imaging monitoring of intestinal failure

Timing	Imaging investigations
At PN beginning	*Chest X-ray*: (a) when the position of the tip has not been checked during the procedure and/or (b) when the device has been placed using blind subclavian approach or other techniques which carry the risk of pleuropulmonary damage
Each 6 months–1 year	*Abdominal and neck vessels ultrasonography, echocardiography*
Each year	*Bone densitometry*
If indicated	*Chest X-ray, neck vessel ultrasonography, echocardiography, and venography*: if signs or symptoms suggestive for CVC occlusion and/or pain, swelling of the arm and neck, edema, and discoloration of the arm *Gastrointestinal endoscopy/ colonoscopy*: if blood in stool and iron deficiency *Small bowel X-ray transit*: if signs and symptoms of SBBO

PN parenteral nutrition, *CVC* central venous access, *SBBO* small bowel bacterial overgrowth

Conclusions

Nutritional workup of pediatric IF is usually complex and requires close attention. It should be tailored to the single case. The outcome is significantly improved if they are managed by a multidisciplinary team that allows for fully integrated care of inpatients and outpatients with IF by favoring coordination of surgical, medical, and nutrition management [1, 5, 6].

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Short Bowel Syndrome: Pharmacological Improvement of Bowel Function and Adaptation

6

Palle Bekker Jeppesen

Abbreviations

Abd. Dist	Abdominal distension
Abd. Pain	Abdominal pain
BID	Twice daily
CD	Crohn's Disease
EJIS	End jejunostomy or ileostomy
GH	Growth hormone
GI	Gastrointestinal
GLP	Glucagon-like peptide
Hab	Habitual
HCLF	High carbohydrate low fat
HPN	Home parenteral nutrition
IF	Intestinal failure
INS	Intestinal insufficiency
IRA	Ileorectal anastomosis
ITA	Ileotransverse anastomosis
JRA	Jejuno-rectal anastomosis
Mth	Month
NM	Not measured
NR	Not reported
NS	Non-significant
OD	Once daily
OLCS	Open-label case series
ORS	Oral rehydration solutions
PPI	Proton-pump inhibitor
PS	Parenteral support
RCT	Randomised controlled trial
SB	Small bowel
SBS	Short bowel syndrome
TID	Three times daily
Unk	Unknown
y	Years
Δ	Compared to baseline

P.B. Jeppesen
Department of Gastroenterology, Rigshospitalet, Copenhagen, Denmark
e-mail: Palle.Bekker.Jeppesen@regionh.dk

Basic Understanding of the Pathophysiological Changes in SBS as a Prerequisite for Optimal Treatment

The primary function of the gastrointestinal (GI) tract is the adequate digestion and absorption of nutrients (macronutrients, fluid, electrolytes, trace elements and vitamins) to meet the metabolic requirements of life, thereby preserving nutritional homeostasis, growth, body composition, function and overall health. The intact, healthy GI tract possesses a large reserve capacity for nutrient assimilation (i.e. digestion and absorption) [1]. Indeed, in adults, the net absorption (i.e. dietary intake minus faecal excretion) of macronutrients exceeds 97 %, and the wet weight of faecal material remains below 300 g/day even after a substantial increase in oral intake.

In patients with short bowel syndrome (SBS), based on the severity of the underlying pathophysiological condition or disease, a spectrum

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from mild, moderate and severe intestinal insufficiency (INS) across a borderline to mild, moderate and severe intestinal failure (IF) may exist [2]. Absolute intestinal absorption may be impaired by intestinal resection and a reduction in the absorptive surface area, but a variety of other pathophysiological conditions may contribute to the development of IF [3]. Examples include extensive mucosal disease caused by inflammatory bowel disease, radiation enteritis, coeliac disease or microvillus atrophy. Furthermore, the absorptive surface area may be bypassed by the presence of intestinal fistula. In addition, intestinal obstruction or pseudo-obstruction could diminish the oral intake of the patient, thereby limiting their capacity for compensatory hyperphagia. Nutrient assimilation could also be diminished by impairment of digestion caused by disturbances in the production of bile acids [4] and digestive enzymes [5]. Small intestinal bacterial overgrowth could also contribute to the malabsorptive disorder [6, 7]. In addition, it has also been suggested that the neuroendocrine feedback, evidenced by the elevated [8] or impaired [9] postprandial endogenous hormone secretions, in SBS patients with and without an intact "ileo-colonic" brake, respectively, could play a central role in the regulation of the gastrointestinal motility, gastric and intestinal secretion, and the functional adaptation following surgery. Thus, these potential pathophysiological factors should be considered and addressed when evaluating and treating SBS patients with IF. The location of the individual SBS patient in the spectrum from intestinal insufficiency to intestinal failure may depend upon all of these factors, the ability of the patient to compensate for this malassimilation, the metabolic needs of the patient and the ability and willingness of the patient to adapt to a situation with limited nutrient availability.

By definition, patients with IF need parenteral support (PS) to ensure the adequate provision of macronutrients and/or water and electrolytes, while the patients with INS can compensate orally by hyperphagia to manage without [10].

Type 1 and 2 IF patients require PS temporarily while regaining intestinal function and restoring nutritional deficits and metabolic instability following surgery, whereas the need for PS may be permanent in type 3 IF patients depending on the degree of functional intestinal adaptation [11]. These patients are discharged from the hospital with home parenteral nutrition (HPN). If left untreated, the type 3 IF patients will experience depletion of their body stores and changes in body function and clinical symptoms, and they may eventually die due to malnutrition, dehydration and electrolyte disturbances.

In clinical practice, it is important to assess where in the INS/IF spectrum each patient is situated, both to provide the best tailor-made and well-tolerated parenteral support and in order to be able to predict the potential effects and consequences of rehabilitative treatments. Individualised evaluations are required in a syndrome with a large inter-patient variability and large treatment effect heterogeneity. However, this clinical assessment can be difficult or even impossible without objective or indirect measurements of intestinal function. The conduction and evaluation of laboratory blood tests and nutritional screenings and obtaining a careful anamnesis including information regarding the remnant bowel anatomy may provide some guidance, but frequently judgements based on this information are too imprecise to guide potential lifelong treatments.

Previously, measurement of the faecal fat excretion, in relation to consuming a diet with fixed amount of fat, was considered the golden standard regarding measurement of malassimilation. However, this technique has been demonstrated to be a poor predictor of the total faecal energy losses, due to the considerable colonic carbohydrates and protein salvage seen in SBS patients with a preserved colon in continuity [12].

In an attempt to objectively demonstrate the spectrum of malassimilation, Jeppesen and Mortensen measured the absolute intestinal absorption by performing metabolic balance studies in adult patients with intestinal insufficiency and failure [10]. Duplicate portions of oral intakes and faecal excretions were quantified, and absolute energy and wet weight absorption were determined. The results of these balance

studies allowed the spectrum of intestinal insufficiency or failure to be determined and objective discrimination between the two conditions was made possible [10]. These balance studies, however, also illustrated the heterogeneity of the patients within the spectrum. Functional intestinal failure was present in most adult patients when absolute wet weight absorption (diet wet weight minus faecal wet weight) was below 1.4 kg/day (equivalent to 23 g/kg body weight/day) or when absolute energy absorption was below 5 MJ/day [~1200 kcal/day] (~84 % of calculated basal metabolic rate). This wet weight and energy absorption was the minimally required for just maintaining perspiration, renal function and protein-energy metabolism in SBS patients. Based on results from these and other balance studies, a urine volume above 800 mL/day with a sodium concentration above 20 mmol/l and a body mass index above 20 kg/m^2 is desired in adults with SBS [13, 14]. Therefore, today, metabolic balance studies with measurements of the total wet weight and energy intake and excretion by weight measurements and bomb calorimetry, respectively, should be regarded as the golden standard to assess intestinal wet weight and energy absorption in patients with SBS.

Pharmacological Treatment Principles

Employing pharmacological treatments, it is of importance to evaluate and balance the benefit or clinical meaningfulness of interventions versus the inconveniences, adverse effects, risks and cost.

Until recently, the non-surgical treatment principles in SBS patients have mainly built on results from uncontrolled, nonrandomised, open-label patient series. In general, these case series have been investigating various theoretical aspects of pathophysiological features of the short bowel syndrome. Consequently, the general treatment practice has relied on a conjunction of these experiences thereby aiming to maximise intestinal digestion and absorption by a tandem, multidimensional approach.

In theory, the optimisation of intestinal digestion and absorption is achieved by maximising the exposure of the mucosal surface area to nutrients, fluids, electrolytes, trace elements and vitamins in the right form, concentration and composition, at the right place, in the right environment and in a timely fashion. The pathophysiological hallmarks of enterectomy are gastric hypergastrinaemia and hypersecretion [15], accelerated gastric emptying, reduced portal blood flow, impaired immunological and barrier functions and mucosal replacement, repair and adaptation. The aetiology of these pathophysiological changes in the bowel function presumably involves the loss of secretion of neuroendocrine inhibitors confined to the terminal ileum and colon. Thus, whereas the conventional treatments mainly consist of anti-secretory drugs and anti-motility/antidiarrhoeal drugs, the new hormonal treatments aim to ameliorate these effects by restoration or amplification of the neuroendocrine communication in the gut.

Conventional Pharmacological Treatments

Anti-secretory Drugs

H_2-Receptor Antagonists and Proton-Pump Inhibitors

The gastric hyperacidity, mainly seen in SBS patients with distal bowel resection, may denature pancreatic enzymes [16] and compromise bile salt function [17]. In addition, the sheer volume of the gastric hypersecretion may flush the upper bowel, minimise time for absorption and thereby contribute to the total faecal losses. The treatments for gastric hypersecretion are H_2-receptor antagonists and proton-pump inhibitors (PPIs), but the more potent effect of PPIs on acid suppression has favoured their use. H_2-receptor antagonists and PPIs have also been suggested to delay gastric emptying rates, which possibly also could benefit intestinal absorption in SBS patients [18].

The first clinical use of acid suppression in SBS patients was described by Cortot et al. [19]

and subsequently by Murphy et al. [20]. They found that gastric output of hydrogen ion was significantly greater than in controls in the early postoperative period and that cimetidine given orally and intravenously reduced the fractional gastric emptying of water and decreased gastric volume and acid output by around 50 %, which subsequently reduced stomal losses.

The results of subsequent open-label case series and randomised controlled trials are given in Table 6.1. In three studies, i.v. H_2 blockers were employed, whereas proton-pump inhibitors were given either orally or intravenously in each of the two last studies. In general, the studies were acute, short term (less than 7 days) and mainly performed in SBS patients with an end jejunostomy or ileostomy. The majority of the patients had a stomal wet weight output exceeding 2000 g/day, and 26 out of 40 patients received PS. The absolute reductions in faecal wet weight excretions in relation to treatments varied between studies from 420 to 886 g/day corresponding to decreases in the relative wet weight excretion of 12–27 %. This was parallelled by reduction in stomal sodium losses of 20–62 mmol/day corresponding to reductions of 8–27 %. In one of the studies, an effect on macronutrient absorption was demonstrated. The positive effects on wet weight and sodium absorption were demonstrated not only in the immediate postoperative period but also in patients who had had surgery up to 11 years earlier. The largest absolute effects were seen in patients with the highest wet weight outputs, and clinically relevant effects were mainly seen in patients with a stomal output exceeding 2.5 kg/day. Frequently, the degree of absorption of PPIs is unknown in SBS-IF patients, and in case of lack of effect of tablets and capsules, soluble forms of esomeprazole (40 BID) or intravenous administration should be considered. This would be the case in most SBS patients with less than 60 cm of jejunum. A stomal pH of at least 6 is desired. In general, the patient-reported side effects in relation to the use of H_2 blockers and proton-pump inhibitors were limited, but a few patients reported "colicky" abdominal pain in relation to PPI treatment.

Somatostatin and Octreotide

Somatostatin has been demonstrated to possess beneficial effects in the treatment of chronic diarrhoeal conditions. Somatostatin is a neurotransmitter produced by the hypothalamus, a peptide hormone found in pancreatic D cells, and it is widely distributed in the neuroendocrine cells throughout the gastrointestinal tract. Somatostatin has been suggested to decrease gastric [25], biliary and pancreatic secretions [26–28]. In addition, it may inhibit secretagogue-induced water and electrolyte secretion in the jejunum and the colon [29], stimulate sodium and chloride absorption in the ileum [30], decrease intestinal motility [31] and inhibit the release of hormones that may contribute to diarrhoea (e.g. VIP, GIP, gastrin) [32].

Dharmsathaphorn et al. were the first to report the acute effects of a 24-h infusion of somatostatin, at a rate of 4 ug/min, in four patients with SBS due to multiple resections for Crohn's disease [33]. A total colectomy was performed in three out of four patients and their remnant jejunum was less than 10 ft. All antidiarrhoeal medications were withdrawn 2 days before admission, and patients were placed on a standardised 2000 kcal diet containing 75 g/day of fat. Somatostatin infusion induced a reduction in stool weight in all four patients (from 1892 ± 241 g/day to 1236 ± 254 g/day, on average corresponding to 35 %, $p < 0.05$). Reductions in faecal excretions of electrolytes and macronutrients were all non-significant. GIP and peptide PP levels were suppressed by the somatostatin infusions. Infusions were well tolerated and no symptoms or complications were described in relation to the treatment. However, a rebound effect was noted immediately after cessation of infusions.

The use of a long-acting somatostatin analogue, SMS 201–955 (octreotide), with an extended half-life of 3–4 h (compared to a few minutes in the native peptide) was first reported in a 46-year-old woman with Crohn's disease for which she had undergone a colectomy and subsequently removal of an ileorectal anastomosis. Due to an ostomy output of 4–6 l per day, she required PS. In relation to 24-h of infusions of SMS 201–955 (25 ug/h) 4 months after the

Table 6.1 Summary of H_2-receptor antagonist and proton-pump inhibitor studies and results

	Aly et al. [21]	Jacobsen et al. [22]	Nightingale et al. [23]	Jeppesen et al. [24]	Jeppesen et al. [24]
Study type	RCT	OLCS	OLCS	RCT	RCT
Cimetidine	400 mg QID i.v.	400 mg QID i.v.	40 mg OD p.o.	150 mg BID i.v.	40 mg BID i.v.
Ranitidine					
Omeprazole					
Duration	7 days	2 days	2 days	5 days	5 days
No. pts	10 (all CD)	8 (6 CD)	11 (8 CD)	11	11
SBS type	8 EJIS, 1 ITA, 1 IRA	8 EJS,	10 EJS, 1 JRA,	11 EJIS,	11 EJIS,
	30–300 cm SB resection	Remnant SB median 120 cm (60–220)	Remnant mean SB length 86 cm (25–140)	Remnant SB Median 125 cm	Remnant SB Median 125 cm
Time from last surg.	4.5 y (1–11 y)	PS for 1–42 mths	56 mths (1–312)	3.8 y (2.5–4.7)	3.8 y (2.5–4.7)
Baseline faecal weight	2479 g/day	3864 g/day	3820 g/day	2925 g/day	2925 g/day
	(618–5556)	(2133–8500)	(1480–8250)	(1740–4565)	(1740–4565)
Baseline faecal sodium	229 mmol/day	316 mmol/day	308 mmol/day	248 mmol/day	248 mmol/day
	(27–498)	(207–591)	(148–497)	(131–438)	(131–438)
PS	None	8 of 8	8 of 11	10 of 11	10 of 11
Follow-up faecal weight	1933 g/day	2978 g/day	3335 g/day	2468 g/day	2388
		(1295–5890)	(1360–8020)	(1563–4563)	(1550–3770)
ΔFaecal weight	−545 g/g ~ −22 %	−886 g/day ~ −23 %	−485 g/day ~ −12 %	−420 g/day ~ −14 %	−630 g/day ~ −27 %
ΔFaecal sodium	−62 mmol/day ~ −27 %	−55 mmol/day ~ −17 %	−32 mmol/day ~ −10 %	−28 mmol/day ~ −8 %	−20 mmol/day ~ −18 %
ΔUrine volume	NS	674 ml/day	–	NS	NS
		(28–1760)			
ΔUrine sodium	NS	NS	–	NS	+31 mmol/day
Effect on macronutrient abs.	NS	NS	NS	NS	NS

BID twice daily, *CD* Crohn's disease, *EJIS* end jejunostomy or ileostomy, *IRA* Ileorectal anastomosis, *ITA* ileotransverse anastomosis, *JRA* jejuno-rectal anastomosis, *mth* month, *NS* non-significant, *OD* once daily, *OLCS* open-label case series, *PS* parenteral support, *RCT* randomised controlled trial, *SB* small bowel, *TID* three times daily, *unk* unknown, *y* years

creation of the ileostomy, the output decreased from 5300 to 1600 g/day, sodium excretion from 656 to 162 mmol/day and potassium from 48 to 20 mmol/day. The faecal excretion of fat and glucose was not affected. Small bowel transit time was prolonged from 76 to 134 min. Subsequently, the patient was given octreotide, 50 ug subcutaneously twice daily, and her stomal output remained below 2.5 kg/day thereby rendering parenteral support unnecessary [34].

The results of subsequent open-label case series and randomised controlled trials are given in Table 6.2. In the four studies employing octreotide, mainly patients with end jejunostomy with true high outputs, evidenced by average stomal losses exceeding 4 kg/day and needs for PS exceeding 3 l/day, were examined. In these patients, a 30–40 % reduction in wet weight and sodium losses was demonstrated. Again, the largest effects seemed to be confined to the patients with the highest outputs. It was not possible to demonstrate significant positive effects on the macronutrient absorption in relation to octreotide treatment. In other studies, the actual data in relation to octreotide treatment on reductions in stomal output were not presented [41] or only presented in abstract form [42, 43]. However, the main conclusions in these studies were in accordance with the other studies.

In general, a few patients developed abdominal distention, cramping and symptoms of ileus that resolved after conservative treatment and discontinuation of octreotide. Labile blood sugars, symptoms of fluid overload (oedema and headache) and formation of gallstones necessitating cholecystectomy were described in relation to long-term octreotide treatment. Somatostatin may reduce splanchnic blood flow [44], and concerns have been raised by O'Keefe et al. that long-term octreotide treatment would interfere with the process of intestinal adaptation [38, 39, 45]. Therefore, in recent recommendations, a careful monitoring of patients is advised in patients treated with octreotide to prevent fluid retention in relation to initiation of the treatment as well as potential adverse effects and potential negative interference with the process of intestinal adaptation in the long-term use.

In the last study given in Table 6.2, Nehra et al. described the use of a long-acting release depot, octreotide preparation, Sandostatin LAR, in a 15-week, open-label trial in eight adult SBS-IF patients [40]. Following the initial 48-h balance study, the patients received the first 20 mg, intramuscular, Sandostatin LAR injection. This was repeated by self-injection as an outpatient at weeks 3, 7 and 11. The parenteral support was kept constant throughout the study, and patients had a fixed habitual-like diet during admissions. Sandostatin LAR treatment did not lead to significant differences in body weight, 48-h urine volume, stool weight, faecal sodium or potassium losses or faecal fat excretion. This suggests that peak concentrations rather than the area under the curve may be important for the effect of Sandostatin and analogues.

Clonidine

Clonidine is approved by the FDA and EMA to treat hypertension. It is an α_2-adrenergic receptor agonist that also inhibits gastrointestinal motility by both central and peripheral actions. It increases intestinal sodium and water absorption and decreases bicarbonate secretion by direct activation of postsynaptic enterocyte α_2-adrenoreceptors [46, 47].

The effect of clonidine was initially described in a patient with refractory diarrhoea (up to 10 l/day) following colectomy and placement of an ileostomy. The patient was treated with clonidine, after failure in treatments with loperamide, tinctura opii, cholestyramine and somatostatin to reduce stool volume to less than 6 l/day. Under combined treatment with clonidine (1200 micrograms/day) and somatostatin (6 mg/day), which was well tolerated, stool weights were normalised within 24 h [48]. McDoniel et al. described the effect of clonidine in two other SBS patients [49], and Buchmann et al. subsequently described the effect of clonidine in eight jejunostomy SBS patients (small bowel length 72 ± 152 cm) before and after placement of a 0.3 mg clonidine patch for a week [50]. This resulted in a reduction in the faecal weight of 438 ± 527 g/day (9.4 %, $p = .05$, baseline 4394 ± 1727 g/day). Urine volumes correspondingly tended to increase by 747 ± 1934 mL/day (18.9 %, $p =$ not significant).

Table 6.2 Summary of octreotide studies and results

	Rodrigues et al. [35]	Nightingale et al. [36]	Ladefoged et al. [37]	O'Keefe et al. [38, 39]	Nehra et al. [40]
Study type	OLCS	OLCS	RCT	OLCS	OLCS
Octreotide/Sandostatin LAR	Octreotide 50 µg s.c. 30 min Before-test meal	Octreotide 50 µg i.v. BID	Octreotide 25 µg/h i.v. or 50 µg s.c. BID	Octreotide 100 µg s.c. BID	Sandostatin LAR 20 mg depot at 0, 3, 7 and 11 weeks
Duration	6 h	2 days	2 days	11 days	15 weeks
No pts	4	6	6	10	
SBS type	3 EJIS, 1 JR anast. Remnant SB 30–100 cm	5 EJIS, 1JR anast. Remnant SB 25–70 cm	6 EJIS Remnant SB: 40, 100, 110, 150, 225, All 30 cm	10 EJS Remnant SB 15–200 cm	5 EJIS 3 SBS + colon
Time from last surg.	2–75 mths	unk	14–101 mths	1–15 years	11.1 years on TPN (range 1–22 y)
Baseline faecal weight	0.923 ± 0.213 kg/6 h	5.13 kg/day (3.6–6.9)	4.92 kg/day (2.3–8.2)	8.1 ± 1.8 l/day (2.4–20.7)	4.54 kg/day (2.20–10.72)
Baseline faecal sodium	95 ± 12 mmol/6 h	405 mmol/day	347 mmol/day (144–601)	510 ± 71 mmol/day (247–982)	393 mmol/day (126–789)
PS	All 4	All 6, PS volume > 4.5 l/day	All 6 > PS volume > 4.5 l/day	PS volume > 3 l/ in 9 of 10 pts	All 8
Follow-up faecal weight	0.358 ± 0.078 kg/6 h	3.30 kg/day	unk	unk	4.63 kg/day (2.24–11.16)
ΔFaecal weight	−0.565 kg/6 h (~ −39 %)	−1.83 kg/day (0.5–5.0 kg/day, ~ −36 %)	i.v.: Abs. increase= 1.12 kg/day (0.35–1.85 g/day, ~29 %) s.c.: Abs. increase= 1.37 g/day (0.64–2.11 g/day ~ 36 %)	−3.3 ± 0.4 l/day (~ −41 %)	+0.10 kg/day (−0.66 to 0.99, ~2 %)
ΔFaecal sodium	−46 mmol/6 h	−157 mmol/day (−56 to −405 mmol/day, ~ −39 %)	i.v.: Abs. increase= 126 mmol/day (52–191 mmol/day ~ 87 %) s.c.: 115 mmol/day (16–142 mmol/day ~ 79 %)	−170 mmol/day (~ −33 %)	−10 mmol/day (~ −3 %)
ΔUrine volume	–	unk	unk	NS	
ΔUrine sodium	–	unk	unk	unk	
Effect on macronutrients abs.	NS	NS	NS	NS	

BID twice daily, *CD* Crohn's disease, *EJIS* end jejunostomy or ileostomy, *IRA* ileorectal anastomosis, *ITA* ileotransverse anastomosis, *JRA* jejuno-rectal anastomosis, *mth* month, *NS* non-significant, *OD* once daily, *OLCS* open-label case series, *PS* parenteral support, *RCT* randomised controlled trial, *SB* small bowel, *TID* three times daily, *unk* unknown, *y* years

Faecal sodium loss decreased by 887 ± 996 mg/day (11.2 ± 12.3 %; $p = 0.036$). None of the patients developed hypotension, and in short-term studies, the adverse events were minor.

Anti-motility/Antidiarrhoeal Drugs

As given in Table 6.3, oral loperamide and codeine phosphate reduce intestinal motility and decrease fluid and sodium output from ileostomies by 20–30 % [55, 56]. Loperamide, 4 mg given four times per day, has been shown to be superior to codeine phosphate, 60 mg four times per day, in reducing the weight and sodium content of ileostomy fluid [53, 57]. Loperamide is, however, circulated through the enterohepatic circulation, and therefore doses as high as 12–24 mg at a time may be required in patients with resection of the terminal ileum. A mixture of codeine phosphate (8 mg/ml) in doses as high as 80–160 mg or tincture of opium, 0.3–1.0 mL, both four times per day, is employed in other centres. The optimal timing, dose and tolerability of all of these drugs may be highly individual. They are often used in combination, and it is suggested that they should be provided 30–60 min before meals and at bedtime, although the scientific evidence for this practice is lacking. In general, the effect of the anti-motility and antidiarrhoeal drugs has been demonstrated in patients with a faecal excretion of less than 1000 g/day (Table 6.3), and the effects in high-output situations are not well described. Therefore, in the ideal setting, the clinical effects on symptoms and faecal excretions should be evaluated in the individual patient, especially in the light of detrimental sedative and possible addictive, central effects of codeine and opium.

The Use of Intestinal Growth Factors and Mediators of Intestinal Adaptation

The search for the main factors responsible for the intestinal adaptation seen in some SBS patients following intestinal resection has triggered the use of hormones to promote "bowel rehabilitation". The pathophysiological effects of intestinal resection on gastrointestinal motility, secretion, blood flow, immunological and barrier functions, mucosal replacement, repair and adaptation may be ameliorated by restoration or amplification of the neuroendocrine communication in the gut. This structural and functional adaptation, or even a degree of hyperadaptation, may be induced by luminal stimulation of the endogenous gastrointestinal hormone secretion, by the amplification of this secretion by reducing hormone degradation or by exogenous hormonal therapy. Growth hormone, glucagon-like peptide-2 and the analogue, teduglutide and GLP-1 have been investigated in clinical trials.

Growth Hormone

A summary of growth hormone studies and results is given in Table 6.4. Byrne and Wilmore were the first to use high-dose (0.14 mg/kg/day) growth hormone, glutamine, and a high-carbohydrate diet in the treatment of short bowel patients [58, 66]. When combining these treatment modalities in SBS patients with a preserved colon, who on average had a faecal wet weight excretion of 1.65 kg/day, the wet weight absorption increased from 1.7 to 2.4 kg/day, and sodium absorption increased from 74 to 113 mmol/day over 5 weeks of treatment. However, in addition to dietary changes toward a high-carbohydrate diet, all eight patients were also given oral rehydration solutions as a part of the "rehabilitation". Therefore, the true effects of growth hormone were challenged by Scolapio et al. [60, 61] and Szkudlarek et al. [62, 63], who could not replicate the positive effects on wet weight or energy absorption in a more mixed patient population with a more severe intestinal failure. In the lower-dose studies from Ellegaard et al. (growth hormone, 0.024 mg/kg/day) [65] and Seguy et al. (0.05 mg/kg/day) [64], no significant positive effects on either wet weight or sodium absorption were seen. In the study by Seguy et al., growth hormone and an unrestricted hyperphagic diet increased intestinal nitrogen absorption by 146 %

Table 6.3 Summary of antidiarrhoeal studies and results

	Tytgat et al. [51, 52]	Tytgat et al. [53]	Mainguet et al. [54]	Newton et al. [55]	King et al. [56]
Study type	RCT	RCT	RCT	OLCS	RCT
Treatment	Loperamide 4 mg BID 3 days Loperamide 4 mg TID 4 days	Loperamide 4 mg TID	Loperamide 4–12 mg, median 6 mg	Codeine 60 mg TID	Loperamide 4 mg TID vs. codeine 60 mg TID
Duration	7 days	7 days	Median 37 days	5 days	4 days each
No. of patients	20	7	13	5	9
SBS type	Ileostomies: 12 UC, 5 CD, 1 AC, 1 CP	Ileostomies: 4 UC, 2 CD, 1 CP	Pts with ileocolic resections	Ileostomies due to IBD	Ileostomies: 6 UC and 4 CD with <60 cm SB resection
Time from last surg.	26 mths (3 mths–25 y)	3 y (27 mths–10 y)	unk	2.3 y (2 mths–7y)	6.2 y (2–15y)
Baseline /placebo faecal weight	Median 660 Mean 698 g/day (range 180–2020)	716 g/day (range 409–1158)	800 g/day	991 g/day (approx. 600–1300)	633 ± 253 g/day (range 367–819)
Baseline faecal sodium	–	121 mmol/day (51–199)	–	131 mmol/day (approx. 90–190)	76 ± 38 mmol/day
Follow-up/active treatment faecal weight	Median 500 g/day Mean 557 g/day	481 g/day (286–1158)	480 g/day	755 g/day	Lop: 464 ± 116 g/day, Cod: 524 ± 200 g/day
Follow-up/active treatment faecal sodium		47 mmol/day (27–156)	–	99 mmol/day	Lop: 47 ± 15 mmol/day, $p < 0.02$ Cod: 60 ± 25 mmol/day, NS
ΔFaecal weight	Mean −141 g/day (40–344) ~ −20 % (80–2010)	−33 %	Approximately – 320 g/day ~ 40 %	−236 g/day (approx. 40–350)	Lop: −169 g/day ~ −27 % Cod: −109 g/day ~ −17 %
ΔFaecal sodium	–	NS (-21 %)	–	−32 mmol/day	Lop: −30 mmol/day ~ −39 % Cod: −16 mmol/day ~ −21 %
ΔFaecal macronutrients	–	Lipid NS	–	Increase fat 13 g/day	Lop: Increase fat 4 g/day Cod: Increase 2 g/day, NS

None of the patients received parenteral support. In one of the studies, measurements of urine volume or electrolytes are provided. *BID* twice daily, *CD* Crohn's disease, *EJIS* end jejunostomy or ileostomy, *IRA* ileorectal anastomosis, *ITA* ileotransverse anastomosis, *JRA* jejuno-rectal anastomosis, *mth* month, *NS* non-significant, *OD* once daily, *OLCS* open-label case series, *PS* parenteral support, *RCT* randomised controlled trial, *SB* small bowel, *TID* three times daily, *unk* unknown, *y* years

Table 6.4 Summary of growth hormone studies and results

	Drug/ dose (mg/kg/day)	Days	Diet	Glutamine i.v./p.o	ORS	Pts with CD (n/ total)	Remnant small bowel (cm)	Colon in continuity (n/total)	Δ PN volume (kg/ day)	ΔWet weight abs. (kg/ day)	ΔPN energy (kcal/day)	ΔEnergy abs. (kcal/day)	ΔBody weight (kg)	Oedema	Arthralgia/Abd. Dist./Abd. Pain/ nausea
Byrne et al. [58, 59]	GH/0.14	21	HCLF	.42 g/kg/day or .62 g/kg/day	Yes	1/8	37 ± 27	8/8	Fixed	0.7	Fixed	141	5.4	NR	NR
Scolapio et al. [60, 61]	GH/0.14	21	HCLF	0 g/day and .63 g/kg/day	No	7/8	71 ± 23	2/8	Fixed	NR, n.s.	Fixed	NM	3.0	100 %	12 %/NR/ NR/12 %
Szkudlarek et al. [62], Jeppesen et al. [63]	GH/0.12	28 (+5)	Hab	5.2 ± 2.2 g/day and 28 ± 2 g/day	No	6/8	104 ± 37	4/8	Fixed	−0.3, n.s.	Fixed	−72 n.s.	1.0	100 %	75 %/NR/ NR/12 %
Byrne et al. [59]	(a) Placebo	28	HCLF	0 g/day and 30 g/ day	Yes	1/9	62 ± 31	8/9	−0.54	NM	−376	NM	−0.7	11 %	0 %/ NR/11 %/0 %
	(b) GH/0.10	28	HCLF	0 g/day and 30 g/ day	Yes	2/16	84 ± 50	15/16	−0.84	NM	−620	NM	1.2	69 %	44 %/ NR/25 %/13 %
	(c) GH/0.10	28	HCLF	0 g/day and 30 g/ day	Yes	5/16	68 ± 33	13/16	−1.10	NM	−822	NM	1.8	84 %	31 %/ NR/13 %/31 %
	(a) vs. (c)	28	HCLF	–	Yes	–	–	–	−0.56, $p < 0.05$	NM	−445, $p < 0.001$	NM	2.5, n.s.		
Seguy et al. [64]	GH//0.05	21	Hab	0 g/day and 0 g/ day	No	3/12	48 ± 11	9/12	Fixed	NR, n.s.	NM	102	2.4	0 %	8 %/NR/NR/NR
Ellegaard et al. [65]	GH/0.024	56	Hab	0 g/day and 0 g/d	No	8/8	125 ± 29	5/10	Fixed	NR, n.s.	Fixed	NR, n.s.	2.3	0 %	0–37 %/ NR/12 %/12 %

Abd. Dist. abdominal distension, *Abd. Pain* abdominal pain, *CD* Crohn's disease, *Hab* habitual, *HCLF* high-carbohydrate low fat, *NM* not measured, *NR* not reported, *n.s.* not significant, *ORS* oral rehydration solutions, Δ compared to baseline

($p<0.040$), carbohydrates by 104 % ($p<0.040$) and energy by 155 % ($p<0.002$), which in absolute terms was 427 kcal/day (~1787 kJ/day). Fat absorption was unaffected by the treatment. During growth hormone treatment, the mean dietary energy intake was 192 kcal/day (804 kJ/day) higher. Ultimately, the efficacy of somatotropin (0.1 mg/kg/day for 4 weeks) was tested in a randomised, double-blind, parallel-group, pivotal study of 41 patients with short bowel syndrome (mainly with a preserved colon and stool volume less than 3 L/day), who were dependent on parenteral nutrition [59]. The protocol for weaning from parenteral support is not given, but it mainly seems to be based on body weight, measurement of total body water by BIA and measurements of serum sodium, potassium and bicarbonate. A significant greater reduction from baseline in total parenteral volume occurred in recipients of somatropin (Zorptive™) plus glutamine or somatropin (Zorptive™) alone than in placebo plus glutamine recipients (–7.7 and –5.9 vs. –3.8 L/week). Thus, the effect of somatropin and glutamine averaged 557 ml/day. Balance studies on intestinal absorption were not performed and the results on urinary excretions were not given [59]. The mean reductions from baseline in total parenteral calories were significantly greater in recipients of somatropin plus glutamine or somatropin alone than in recipients of placebo plus glutamine 5751 and 4338 vs. 2633 kcal/week. Thus, the effect of the combined therapy of somatropin plus glutamine would correspond to an effect of 445 kcal/day (1863 kJ/day). Apparently, there were no changes in the dietary energy intake in the three parallel study groups. However, a weight loss of 5.2 kg of body weight (from 63.9 to 58.7 kg) was observed from week 2 (pretreatment) to week 18 (12 weeks post-treatment) in patients treated with the combined therapy of somatropin plus glutamine. This weight loss closely reflected the anticipated weight loss derived by calculation of the energy deficit obtained by reduction of the parenteral energy support of 1863 kJ/day.

The diverging conclusions of the studies of GH in SBS patients reveal the controversial role for GH in this condition [67]. The effects of GH are global and not specific for the intestine. It has been reported that GH increases extracellular volume by stimulating sodium reabsorption in the distal nephron and preventing pressure natriuresis [68]. When using bioelectrical impedance in the weaning from parenteral support, it should be considered that the effects of GH on fluid balance in SBS patients may be related to effects on the kidneys and the extracellular space rather than on the intestine. The positive effect of low-dose GH on energy absorption observed in Seguy's study may be explained by GH acting via IGF-1 mainly in SBS patients with a preserved colon. Alternatively, the GH-induced stimulation of IGF-1 [69] might stimulate GLP-2 effect in the intestine. This assumption is supported by the results from the study by Liu [70], which indicates that IGF-1 may be a downstream mediator of GLP-2 action in intestinal growth. In 2003, the FDA approved Zorptive® for 4-week treatments in SBS patients. However, since none of the studies have demonstrated ongoing effects after termination of treatment, it is likely that effects disappear shortly after discontinuation. The presence and severity of adverse effects (swelling, fluid retention symptoms, myalgia, arthralgia, gynaecomastia, carpal tunnel syndrome, nightmares and insomnia) in relation to high-dose growth hormone treatment have raised concern and may explain the limited long-term use and commercial success of this treatment modality.

Glucagon-Like Peptide 2 and Teduglutide

Another hormone of interest in the treatment of SBS patients is glucagon-like peptide-2 (GLP-2). A summary of GLP-2 and teduglutide studies and results are given in Table 6.5. Initially GLP-2 was highlighted for its effect on the promotion of the expansion of the intestinal mucosa via the stimulation of crypt cell growth and the reduction of enterocyte apoptosis in relation to exogenous GLP-2 administration [75]. However, a wide range of other beneficial physiological effects of GLP-2 have been described.

Table 6.5 Summary of glucagon-like peptide 2 and teduglutide studies and results

Citation	Drug/dose (mg/kg/day)	Days	Diet	Glutamine i.v./p.o	ORS	Pts with CD (n/total)	Remnant small bowel (cm)	Colon in continuity (n/total)	Δ PN volume (kg/day)	ΔWet weight abs. (kg/day)	ΔPN energy (kcal/day)	ΔEnergy abs. (kcal/day)	ΔBody weight (kg)	Oedema	Arthralgia/ Abd. Dist./Abd. Pain/ nausea
Jeppesen et al. [71]	GLP-2/0.013	35	Hab	No	No	6/8	30–180	0/8	Fixed	0.42, $p<0.05$	Fixed	105, $p=0.09$	1.2, $p=0.01$	0 %	0 %/0 %/0 %/0 %
Jeppesen et al. [72]	Teduglutide/0.03–0.15	21	Hab	No	No	11/16	25–150	6/16	Fixed	0.74, $p<0.05$	Fixed	189, n.s.	0.9, $p=0.12$	44 %	NR/ NR/19 %/NR
Jeppesen et al. [73]	(a) Placebo	168 (24 weeks)	Hab	No	No	7/16	77 ± 23	11/16	–0.13, $p=0.03$	NM	–58, $p=0.056$	NM	0.2, n.s.	0 %	0 %/0 %/6 %/6 %
	(b) Teduglutide/0.05	168 (24 weeks)	Hab	No	No	10/35	58 ± 44	26/35	–0.35, $p<0.05$	NM	–218, $p=0.001$	NM	1.2, $p<0.05$	2.9 %	0 %/9 %/6 %/11 %
	(c) Teduglutide/0.10	168 (24 weeks)	Hab	No	No	13/32	68 ± 43	19/32	–0.35, $p<0.05$	NM	–107, $p=0.03$	NM	1.4, $p<0.01$	3.1 %	3.1 %/3 %/3 %/9 %
	(a) vs. (b)	168	Hab	No	No	–	–	–	$p=0.08$	NM	$p=0.11$	NM	$p=0.31$	–	–
	(a) vs. (c)	168	Hab	No	No	–	–	–	$p=0.08$	NM	$p=0.11$	NM	$p=0.18$	–	–
Jeppesen et al. [74]	(a) Placebo	168 (24 weeks)	Hab	No	No	8/43	69 ± 64	23/43	–0.63, $p<0.001$	NM	NM	NM	–0.6, $p=0.20$	5 %	NR/ 2 %/23 %/19 %
	(b) Teduglutide/0.05	168 (24 weeks)	Hab	No	No	10/43	84 ± 65	26/43	0,33, $p<0.01$	NM	NM	NM	1.0, $p=0.10$	17 %	NR/ 21 %/31 %/29 %
	(a) vs. (b)	168	Hab	No	No	–	–	–	$p=0.1$	NM	NM	NM	n.s.	–	–

Abd. Dist. abdominal distension, *Abd. Pain* abdominal pain, *CD* Crohn's disease, *Hab* habitual, *HCLF* high-carbohydrate low fat, *NM* not measured, *NR* not reported, *n.s.* not significant, *ORS* oral rehydration solutions, Δ compared to baseline

Thus, GLP-2 inhibits gastric acid secretion and gastric emptying, stimulates intestinal blood flow [76–78], increases intestinal barrier function [79], opposes inflammatory insults [80, 81] and enhances nutrient and fluid absorption [82], and GLP-2 may also decrease bone resorption [83].

In the first clinical study with native GLP-2 by Jeppesen et al., eight patients were treated with 400 mcg of native GLP-2 twice a day (corresponding to 0.013 ± 0.002 mg/kg/day, a range of 0.011–0.017 mg/kg/day), given subcutaneously for 35 days in an open-label study [71]. None of the patients had colon in continuity. Their average wet weight absorption was 1.2 ± 1.7 kg/day at baseline, and it increased by 420 ± 480 g/day, $p = 0.04$, whereas the effect on sodium absorption did not quite reach statistical significance (33 ± 49 mmol/day, $p = 0.10$).

In a subsequent open-label pilot phase 2 study employing a dipeptidyl peptidase IV-resistant GLP-2 analogue, teduglutide, in doses 0.03–0.15 mg/kg/day, in 16 short bowel patients (6 with remnant parts of the colon), the wet weight absorption increased by 743 ± 477 g/day ($p < 0.001$), thereby significantly increasing urine weight (555 ± 485 g/day, $p < 0.001$) and sodium excretion (53 ± 40 mmol/day, $p < 0.001$) [72]. Teduglutide, in doses 0.03–0.15 mg/kg/day, reduced faecal energy excretion by 808 1453 kJ/day ($p = 0.04$), but this only translated to a significant increase in intestinal absorption (963 1290 kJ/day, $p < 0.05$) in a subset of patients with high dietary compliance during balance studies. No significant changes were seen in the absolute absorption of individual macronutrients [72].

The finding of paralleling increases in urine production related to increases in intestinal wet weight absorption prompted the use of this surrogate endpoint to guide reductions in parenteral support, which were the primary endpoint of the two phase 3, 24-week prospective, randomised, double-blind, placebo-controlled, parallel-group, multinational and multicenter studies conducted in the USA, Canada and Europe [73, 74]. In the first phase 3 study, patients with SBS were randomised to a 0.05 mg/kg/day dose ($n = 35$), a 0.10 mg/kg/day dose ($n = 32$) or placebo ($n = 16$) for up to 24 weeks [73]. Adult SBS patients, mainly with Crohn's disease, vascular disease, volvulus and injury, who had received PS at least three times per week for 12 months were enrolled. PS requirements and oral intakes were optimised and stabilised for up to 16 weeks before randomisation to ensure a constant urine volume between 1 and 2 l per day. In the primary efficacy analysis of the study, no statistically significant difference between the group on teduglutide 0.10 mg/kg/day and the placebo group was shown, while the proportion of subjects receiving the recommended dose of 0.05 mg/kg/day achieved at least a 20 % reduction of parenteral support at weeks 20 and 24 which was significantly higher versus placebo (46 % vs. 6 %, $p < 0.01$). At week 24, teduglutide treatment resulted in a 2.5 L/week reduction in PS requirements from a 9.6 L/week at baseline. In this study, teduglutide also induced expansion of the intestinal mucosa. Sixty-five patients opted to enter an open-label, 28-week extension study [84]. In the patients, who received 1 year of continuous teduglutide treatment, the mean reduction of weekly PS volume was 4.9 l/week equivalent to a 52 % reduction from baseline levels.

After modifications of the study protocol allowing for earlier (at week 2 vs. week 4) and more aggressive PS weaning (10–30 % vs. 10 %), a second pivotal, phase 3 study was performed [74]. Forty-three SBS patients were randomised to a 0.05 mg/kg/day dose of teduglutide, and 43 patients received placebo for up to 24 weeks [74]. The proportion of teduglutide-treated patients achieving a 20–100 % reduction of PS at weeks 20 and 24 was statistically significantly higher compared to placebo (27 out of 43 patients, 62.8 %, vs. 13 out of 43 patients, 30.2 %; $p = 0.002$). Teduglutide treatment resulted in a 4.4 l/week (32 %) reduction in PS volume at week 24 from a pretreatment baseline of 12.9 l/week while maintaining oral fluid intake, urine production and body weight constant throughout the study. In placebo-treated patients, the average PS reductions were 2.3 ± 2.7 L/week (21 %), but they significantly increased their oral fluid intake by 1.6 ± 3.6 L/week ($p < 0.009$) at week 24 in order to maintain urine production constant. In patients completing the study, 21 patients treated

with teduglutide (54 %) versus 9 on placebo (23 %) achieved at least a one-day reduction in PS administration ($p = 0.005$).

The reduction in parenteral energy supply was only reported in the first of the two phase 3 teduglutide studies. Reductions in parenteral energy at week 24 of 243 ± 450 kJ/day ($p = 0.056$), 447 ± 1051 kJ/day ($p = 0.030$) and 912 ± 1333 kJ/day ($p = 0.001$), respectively, were seen in the placebo group, teduglutide 0.10 mg/kg/day group and the teduglutide 0.05 mg/kg/day group, respectively, compared with baseline. However, the reductions in parenteral energy were not significant between active teduglutide (0.10 mg/kg/day and 0.05 mg/kg/day) and placebo ($p = 0.11$) [73].

In all the clinical teduglutide studies, body weights remained stable in spite of PS reductions. Numerical increases in body weight were seen (0.9 ± 2.1 kg, at week 3 [72]; 1.4 ± 2.5 kg, teduglutide 0.10 mg/kg/day and 1.2 ± 2.8 kg teduglutide 0.05 mg/kg/day at week 24 [73]; and 1.0 ± 2.8 kg, teduglutide 0.05 mg/kg/day at week 24 [74]). However, none of these reached statistical significance compared to placebo.

In 2012, the EMA and FDA approved teduglutide (Gattex and Revestive, respectively) for the treatment of SBS patients, and it will probably be available for the clinical use around the world in the years to come. Concern has been raised about potential adverse effects of teduglutide. The phase 3 studies have revealed that teduglutide treatment may be associated with adverse events, mainly of gastrointestinal origin (abdominal distension, abdominal pain, nausea and stoma enlargement), due to its pharmacological mode of action. A carefully monitored down-titration of the daily dose may be considered for some patients with adverse events to optimise tolerability of teduglutide treatment. As a precaution for the development of neoplasia, a colonoscopy with removal of polyps should be conducted at the start of treatment with teduglutide. A re-evaluation at 1 year and adherence to follow-up guidelines are recommended. The use of teduglutide should probably be avoided in patients with active or suspected malignancy and in patients with malignancies in the gastrointestinal tract including the hepatobiliary system within the last 5 years. Cases of cholecystitis, cholangitis, cholelithiasis and pancreatitis have been reported in the clinical studies, and therefore in such cases, continued teduglutide treatment should be reassessed. Causes of intestinal obstruction have been described in clinical studies, and in such incidences, continued teduglutide treatment should be reassessed. Due to the increased fluid absorption in relation to teduglutide, patients with cardiovascular disease should be monitored for cardiac insufficiency or hypertension, especially during initiation of treatment. Patients receiving medicinal products with a narrow therapeutic index should also be monitored due to the potential for increased absorption.

Other Hormones on the Horizon

Numerous growth factors may be involved in the postresectional intestinal adaptation, such as glucagon-like peptide-1 (GLP-1), oxyntomodulin, peptide YY, neurotensin, insulin-like growth factor-1, hepatocyte growth factor, vascular endothelial growth factor, cholecystokinin, epidermal growth factor, gastrin, insulin, vascular endothelial growth factor and keratinocyte growth factor. GLP-2 is just one of many endogenously secreted hormones involved in the process of intestinal adaptation following intestinal resection. Therefore, in theory, other hormones, or inhibitors of their degradation enzymes, individually, or in concert with GLP-2, may have positive effects on the intestinal absorption in SBS patients. Results obtained so far have been demonstrated in preclinical studies and in small, open-label, pilot studies. In mice, inhibiting dipeptidyl peptidase-4 (DPP-4), which is a serine protease cleaving dipeptides from the N-terminal end with l-proline or l-alanine at the penultimate position (e.g. GIP, GLP-1 and GLP-2), has been suggested as a novel approach to promote adaptation in SBS patients with preserved L-cell secretion [85, 86]. Other peptides such as peptide YY, glicentin, oxyntomodulin

and GLP-1 have also been suggested in the treatment of SBS patients. In a small 1-month study, all five consecutive SBS patients with less than 90 cm of small bowel (four with colon in continuity) experienced improvements in stool frequency and form following treatment with the GLP-1 agonist exenatide [87]. Parenteral support was stopped successfully in three of the five patients. Antroduodenal manometry revealed continuous low-amplitude gastric contractions during fasting which completely normalised with exenatide. Likewise, acute effects were observed on intestinal absorption in nine SBS patients (two with colon in continuity) in relation to infusion of native GLP-1 and GLP-2 and co-infusion of GLP-1 and GLP-2 [88]. GLP-1 decreased diarrhoea and faecal excretions in SBS patients, but it seemed less potent than GLP-2. The combination of GLP-1 and GLP-2 numerically provided additive effects on intestinal absorption compared to either peptide given alone.

Conclusion

Given the human distress and healthcare burden associated with severe short bowel syndrome, intestinal insufficiency and failure, better therapies aiming to improve intestinal rehabilitation are needed. Due to the large patient and treatment effect heterogeneity, the ability to objectively measure intestinal absorption becomes a perquisite. It is therefore recommended that more centres include metabolic balance methods for the evaluation of the individual patient and effects of their therapies. Whereas the conventional antisecretory and antidiarrhoeal treatments in general are safe and with limited side effects, the prescription of intestinal growth factors and modulators of intestinal adaptation should be monitored by experts who are experienced in the diagnosis and management of SBS patients. Centres prescribing these agents should have the ability and the facilities to objectively evaluate and balance the benefit and clinical meaningfulness of the interventions versus the inconveniences, adverse effects, potential risks and cost.

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Modern Intestinal Rehabilitation and Outcomes

7

Rubén E. Quirós-Tejeira

Abbreviations

CVC	Central venous catheter
GLP	Glugacon-like peptide
ICV	Ileocecal valve
LCT	Long-chain triglycerides
MCT	Medium-chain triglycerides
PN	Parenteral nutrition
SBBO	Small bowel bacterial overgrowth
SBL	Small bowel length
SBS	Short bowel syndrome
STEP	Serial transverse enteroplasty

Intestinal Rehabilitation

The main goal of any intestinal rehabilitation program is intestinal adaptation, if possible, while optimizing growth and development and trying to maximize enteral nutrition and minimize PN. Although, we are in the era of evidence-based medicine and we continue to learn about long-term PN support and intestinal adaptation, transitioning children from parenteral to enteral nutrition remains as much an art as a science.

For practical clinical purposes, intestinal adaptation is defined as the process by which intestinal absorption is reestablished and PN independency is accomplished. Intestinal adaptation occurs through (a) higher caloric intake; (b) securing a more effective absorption per surface area unit, either by increasing the absorptive surface area (hypertrophy and hyperplasia, with increase in height and diameter of the intestinal villi and increase in crypt depth) or slowing intestinal transit; and (c) normal lengthening process that happens during the first 3–4 years of life [8].

As the majority of patients with intestinal failure have SBS, we need to understand some important factors that help to predict intestinal adaptation and survival to establish a management plan – Table 7.1.

The more practical way to assess the small bowel function after intestinal resection is through enteral feeding tolerance. A study showed that the percentage of enteral feeding tolerated at 3 months post-intestinal resection could predict the probability of becoming PN independent [9]. Children with small bowel length (SBL) of 25 cm with 75 % of their caloric needs delivered enterally would have a 90 % chance of weaning from PN [10]. Conversely, those with < 25 % of calories delivered enterally had a 50 % chance of weaning from PN [11].

R.E. Quirós-Tejeira, MD
Pediatric Gastroenterology, Hepatology and Nutrition, University of Nebraska Medical Center and Children's Hospital & Medical Center, Omaha, NE 68198-2161, USA
e-mail: rquiros@unmc.edu

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Table 7.1 Some important factors affecting intestinal adaptation and survival in short bowel syndrome [9–11]

Better chance	Worse chance
SBL >38 cm	SBL < 15 cm
ICV	No ICV
Intact colon	Colonic resection >50 %
Primary anastomosis	Secondary anastomosis
Intestinal continuity	No intestinal continuity – i.e., ostomy
Liver disease	No Liver disease
>75 % of calories enterally[a]	<25 % of calories enterally[a]

[a]By 3 months post-small bowel resection. *SBL* small bowel length, *ICV* ileocecal valve

Management

Establishing enteral feedings as soon as possible has been widely accepted as one important controllable variable that may help intestinal adaptation [11–13]. Tables 7.2 and 7.3 summarized the management and monitoring of children on PN support.

Parenteral Nutrition (PN) PN has been used for over 30 years allowing long-term survival of children undergoing major intestinal resection [14]. It is important for the parents or guardians to undergo a comprehensive training period, because they will assume full responsibility for CVC and PN care at home. The major nutritional criterion for hospital discharge is evidence of steady weight gain on cycled PN and, in most cases, some enteral feeding [9].

Table 7.2 Management of short bowel syndrome in children

(a) Parenteral nutrition	Main goal is to become PN independent
(b) Enteral nutrition	Focus on "trophic effect" initially
	LCT vs. MCT – LCT promotes intestinal adaptation in animal model If cholestasis, high MCT formulas because bile is not required for MCT absorption
	Continuous vs. boluses – main principle should be to utilize the method that allows the greatest proportion of enteral feedings
(c) Pharmacologic/ medical options	H2 blockers or PPI
	Antimotility agents – to slow down intestinal transit
	Bile salt resin binders – overall, if TI resection
	SBBO with antibiotics (i.e., metronidazole, gentamicin, SMZ/TMP, etc. – enterally)
	UDCA – if TI preserved
	Probiotics – controversial due to potential for bacteremia
	Enteric hormone therapy: GH, GLP-2
(d) SB lengthening procedures	Bianchi procedure vs. STEP in the right candidate
(e) Transplantation	Intestinal vs. liver/intestinal vs. multiorgan

PN parenteral nutrition, *LCT* long-chain triglyceride, *MCT* medium-chain triglyceride, *PPI* proton-pump inhibitors, *TI* terminal ileum, *SBBO* small bowel bacterial overgrowth, *SMZ/TMP* sulfamethoxazole/trimethoprim, *UDCA* ursodeoxycholic acid, *GH* growth hormone, *GLP-2* glucagon-like peptide 2, *STEP* serial transverse enteroplasty procedure

Enteral Nutrition It is extremely important to establish enteral feedings as soon as medically permitted. The initial goal is to have a "trophic effect" with nutrients in the intestinal lumen rather than a concern for calories delivered. In addition, nutrients in the intestinal lumen will be "hepatoprotective" from injuries that PN could cause. Breast milk is always preferred since it may provide growth factor that could help intestinal adaptation [11]. Unfortunately, this is not possible all the time because of different issues including the baby's inability to nipple, the need for tube feedings, and the need for pumping breast milk. In one study, enteral feeding with breast milk or an amino acid-based formula correlated with a shorter PN requirement [12]. In general, the main recommendation is to use elemental or semi-elemental formulas when breast milk is not available since most available studies in children with SBS have used these choices for enteral nutritional support.

Most pediatric gastroenterologists and dietitians would recommend continuous feeding instead of bolus feedings, because of a possible vicious cycle of large-volume feeds and

Table 7.3 Suggested monitoring while on parenteral nutrition

Monitoring	Stool output, growth pattern, and percentage of parenteral support – help to assess intestinal absorption and caloric needs
	Weekly: CBC and differential, AST, ALT alkaline phosphatase, fractioned bilirubin, GGT, albumin, creatinine, BUN, electrolytes, magnesium, calcium, and phosphorus
	Monthly: iron panel and prealbumin
	Every 3 months: Zn, Mn, Se, Cu, Cr
	Every 6 months: vitamins A, D, E, and K. Vitamin B12 overall, if terminal ileum was resected
	Other tests – yearly: liver US, renal US, and bone mineral density testing
	Essential fatty acids profile should be monitored if omega-3 emulsion is used

Actual monitoring should be tailored to each patient's needs based upon clinical status and progress

malabsorptive diarrhea. Overall, there are not well-controlled studies looking at continuous versus bolus feeding. Therefore, the main goal remains to use the method that will deliver the greatest proportion of calories enterally.

Since most children with SBS will require tube feeding, a gastrostomy tube is recommended in most cases. However, it is important to keep in mind that children on tube feedings may not develop good oropharyngeal coordination. Consequently, it is important to allow some oral intake to help developing this skill.

In regard to fat, animal studies have shown that long-chain triglycerides (LCT), especially menhaden oil, have a more significant trophic effect when compared against diets containing short-chain or saturated fat [15]. In the children with cholestasis, it is advisable to use high medium-chain triglycerides (MCT) containing formula, because bile is not required for MCT absorption.

In regard to protein, it has been suggested that intact protein formula may offer a disadvantage to semi-elemental or elemental formula because children with SBS may develop colitis [16]. Although it is not clear if the colitis is due to cow-milk protein allergy or bile acid malabsorption, eliminating cow-milk protein allergy concerns when choosing the formula for these children is not unreasonable.

As far as introduction of meals on children with SBS, it should follow the age-appropriate approach and the estimated absorptive capacity of the children with the main principle of complex carbohydrates being encouraged and refined sugars being discouraged.

Growth Factors and Enteric Hormones One study reported that growth hormone in addition to glutamine increases the height percentile and seemed to facilitate PN independence [17]. There are some other growth factors currently under investigation for their use in promoting intestinal adaptation like glucagon-like peptide 2 (GLP-2) [18, 19]. Clinical use of growth factor in children is still in the investigational phase.

Medications and Intestinal Absorption When treating children with intestinal failure, we have to keep in mind that they may have erratic absorption of enteral medications such as antibiotics. Therefore, IV medications should be considered when treating different conditions such as otitis media.

Gastrointestinal Continuity The presence of colon after intestinal resection is important in adaptation and fluid and electrolyte management. When undigested nutrients reach the colon, they induce changes in the colonic mucosa that enhance water and electrolyte absorption. In addition, mucosal modifications allowing absorption of nutrients such as short- and medium-chain fatty acids take place when the colonic mucosa is exposed to undigested nutrients [20]. Furthermore, intact nutrients reaching the colon will induce enteric hormones like enteroglucagon, peptide YY, GLP-1, and GLP-2 that will promote intestinal adaptation [18, 21, 22]. Therefore, intestinal continuity must be reestablished as soon as possible to enhance the likelihood of intestinal adaptation and PN independency.

Small Bowel Lengthening Procedures The main goal of lengthening procedures is to increase intestinal transit time and subsequently increase

the absorptive surface exposed to nutrients with a subsequent positive impact on absorption and intestinal adaptation. The Bianchi procedure was the first intestinal lengthening technique and was first described in 1980 [23]. In 2003, the serial transverse enteroplasty (STEP) procedure was reported as another alternative for lengthening [2]. A study from our center, University of Nebraska Medical Center, showed that both Bianchi and STEP procedures resulted in improved enteral tolerance, reversed complications of PN, and avoided intestinal transplantation in the majority of patients with reportedly few surgical complications [3]. More recently, including our institution, STEP is becoming more popular since it is technically less complicated than the Bianchi procedure [4]. In any case, a dilated small bowel loop is required for either procedure; therefore, these procedures should only be considered in those children with dilated loop who are not steadily advancing their enteral feeds.

Transplantation In the era of intestinal rehabilitation programs, intestinal or intestinal/liver transplantation is not seen as an end point anymore but as another strategy to accomplish PN independency in the right candidate. This includes children with chronic intestinal failure who have no hope for adaptation, those who have end-stage liver disease, children with CVC access problems, and patients with recurrent CVC-related septic episodes or life-threatening infections. More recently, isolated intestinal transplantation has emerged as a therapeutic option for children with no hope for intestinal adaptation without end-stage liver disease who have central access issues (i.e., SBL < 15 cm without the ICV, long-segment Hirschsprung's disease, etc.).

Avoiding Complications Common complications from PN support are presented in Table 7.4. It is not the purpose of this chapter to discuss in great detail the pathophysiological mechanisms of the PN-associated complications. The most important factor for any intestinal rehabilitation program is to understand and prevent them.

Table 7.4 Common complications of children on parenteral nutrition and short bowel syndrome

Complications
Central venous catheter-related sepsis
Cholestasis progressing to end-stage liver disease
Thrombosis leading to central venous access problems
Small bowel bacterial overgrowth (SBBO)
Gastrointestinal bleeding
Renal disease
Noninfectious colitis
Gallstones
D-lactic acidosis
Dilated intestinal loop
Intestinal strictures or fistulas

CVC-Related Sepsis In our center, we prevent CVC-related sepsis with the careful use of protocolized cleaning techniques and the use of ethanol lock that have had a great impact in our CVC-related septic episodes as it has been reported somewhere else [5]. Prompt treatment of CVC sepsis with antibiotics will also prevent further malabsorption and progression of liver disease caused by possible endotoxemia [24]. Endotoxemia is an important factor that has a negative impact in intestinal adaptation. An animal model of SBS treated with endotoxin has showed a decrease in the intestinal mucosa weight and villus height in the treated rats [25]. Therefore, sepsis will not only worsen liver disease but also may perpetuate intestinal malabsorption in children with intestinal failure.

PN-Associated Liver Disease Different strategies have been well established to prevent liver disease including cycling PN, lipid minimization, avoiding nil per os, special amino acids preparations, preventing CVC sepsis, and, more recently, the possible role of omega-3 fatty acids. Omega-3 fatty acids emulsion has been used to prevent and treat PN-associated cholestasis. One of the principles is that omega-3 fatty acids preparations do not have phytosterols which are present in the soybean emulsion (omega-6 fatty acids). Phytosterols are present at high levels in human serum of individuals on soybean emulsion, and they have been found to contribute to liver disease in experimental animals [26]. Omega-3 fatty

acids have been associated to improvement of cholestasis in children on PN [6], yet further studies are needed to understand the actual role in stopping progression of PN-associated liver disease. Finally, one factor that is frequently overlooked is the restoration of intestinal continuity. Early restoration of intestinal continuity correlates with less severe liver disease [12] and better chance for intestinal adaptation [9, 10].

CVC-Related Thrombosis It is believed that CVC-related thrombosis is related to infection because central vein thrombosis is usually preceded by CVC sepsis and a clot in the CVC. Therefore, prevention and treatment of infection should in theory prevent thrombosis. However, sometimes central venous thrombosis may happen in the absence of infection. In these instances, it could be in relation to increasing tonicity of the PN or "decentralization" of the central access. In addition, hypercoagulable states are not rare, and screening for conditions such as protein S or C deficiency, antithrombin III deficiency, and the factor V Leiden mutation may be helpful.

D-Lactic Acidosis It is another complication in children with SBS. D-lactic acid is normally absent in human serum, but in patients with SBS can be present and causes hyperchloremic metabolic acidosis, encephalopathy, and hypotension. It could be confused with sepsis; however, it is important to recognize that these findings may be in relation to D-lactic acid. D-lactic acid is produced by lactobacilli, bacteroides, and other gram-positive bacteria in the intestine. Treatment includes stopping oral intake of carbohydrates, sodium bicarbonate therapy, enteral administration of poorly absorbed antibiotics (i.e., vancomycin, neomycin, etc.), and thiamine supplementation [27]. D-lactic acidosis is probably secondary to multiple factors including increased small bowel malabsorption, abnormal colonic flora, distorted motility, and impaired lactate metabolism [27–29].

Gastrointestinal (GI) Bleeding Besides the GI bleeding in relation to ulcers in the upper GI tract and portal hypertension, children with SBS could have GI bleeding episodes secondary to ulcers at the anastomotic sites or noninfectious colitis. The intestinal anastomotic bleeding may be related to local ischemia and could be severe enough to require multiple transfusions and surgical revision of the anastomotic site [30]. Sometimes it could be in relation to small bowel bacteria overgrowth (SBBO) and could resolve as SBBO is treated. Noninfectious colitis is probably less common in the current era of hypoallergenic formulas. The prevalence of colitis may be underestimated, as lower endoscopy is not performed routinely in children with SBS. Sulfasalazine (25–50 mg/kg/day) or prednisone (1 mg/kg/day) has been proposed as potential therapeutic options for noninfectious colitis [16].

Outcome

In 1972, Wilmore's report suggested that without the ICV, a jejunoileal segment of more than 38 cm was necessary to ensure survival and that no patient with less than 15 cm of a jejunoileal segment would be able to survive [31]. Fortunately, our understanding of intestinal failure secondary to SBS and the repercussion of long-term PN support have improved significantly over the years. This has had a significant influence in the overall outcome of children with this condition. We still have multiple medical and surgical areas that require further investigation to keep on impacting morbidity and mortality in these children.

One study looked at the chance of becoming PN independent based upon SBL. This study showed that there was a < 50 % chance of becoming PN independent if SBL was < 30 cm, 60 % if SBL was 60 cm or more, and almost 100 % if the SBL was 100 cm [12].

Survival is also affected by SBL. In a 25-year follow-up study, about 80 % of the children with SBL > 15 cm survived vs. 47 % of the ones with SBL < 15 cm. In this study, the impact of the ICV in intestinal adaptation was better appreciated in this latter group, with all the survivors who adapted having the ICV [9]. In the same study,

infants with 15–38 cm of SBL have a reasonable survival and even a good chance for intestinal adaptation with or without the ICV. In addition, the presence of ICV had its greater impact in intestinal adaptation if the SBL was < 15 cm [9].

More recently, we reported a series of 28 children with ultra-SBS (SBL < 20 cm) with 96 % survival and 48 % of them undergoing intestinal adaptation [10]. In this report, there were four children with < 20 cm of SBL without the ileocecal valve who adapted [10] in contrast to a study published 10 years before that showed no children with similar characteristics reaching PN independency [9]. This fact clearly represents the impact that new strategies such as lengthening procedures [2–4], techniques to decrease CVC-related sepsis such as ethanol lock [5], and the use of different lipid emulsions like omega-3 fatty acids [6] and lipid minimization strategies [7] have had in the overall outcome of children with intestinal failure.

Intestinal failure in children on long-term PN remains as one of the most challenging diseases for all health-care providers involved in the care for these patients not only because of the morbidity and mortality involved on it but also due to the financial, emotional, and social burdens to the health-care system and families of these children. Continued research in all different areas of SBS, intestinal failure, and long-term PN support will keep on impacting the care of these children and their overall outcome.

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8 Current Concepts of Intestinal Failure: Serial Transverse Enteroplasty

Mikko P. Pakarinen and Tomas Wester

Abbreviations

AIR	Autologous intestinal reconstruction
IF	Intestinal failure
IFALD	Intestinal failure-associated liver disease
ITx	Intestinal transplantation
LILT	Longitudinal lengthening and tailoring
PN	Parenteral nutrition
PS	Parenteral support
SBS	Short bowel syndrome
STEP	Serial transverse enteroplasty

Background

Pediatric onset intestinal failure (IF) occurs most frequently due to short bowel syndrome (SBS). In children, necrotizing enterocolitis, midgut volvulus, intestinal atresia, and gastroschisis are the most frequent causes for SBS [1, 2]. Due to etiological reasons, bowel resection in SBS patients most often involves the distal small intestine and the ileocecal region including variable length of the colon. The remaining gut adapts to resection by structural and functional changes leading to gradual increase in absorptive capacity per unit length of the small intestine [3, 4]. After resection, dilatation, lengthening, and mucosal hyperplasia compensatorily expand the remaining small intestinal absorptive surface area. Simultaneously, normal small intestinal motility is disrupted [5], which in experimental animals associates with deceleration of transit through the remaining jejunum following distal small bowel resection [6]. Adaptive changes are believed to occur for a large part during the first 2 years after resection, but gradual improvement of intestinal function continues in children alongside with general growth.

In a subset of SBS patients, the small intestinal remnant undergoes excessive dilatation [1]. Dilatation may occur any time after resection but is most commonly observed during the most efficient adaptation period. Abnormal postresectional bowel dilatation predisposes to stasis, defective propulsion, and mixing of intestinal contents, which, in turn, may worsen malabsorption and promote bacterial overgrowth [2, 7]. Based on experimental studies, disruption of normal intestinal motility patterns occurs simultaneously with

M.P. Pakarinen (✉)
Section of Pediatric Surgery, Pediatric Liver and Gut Research Group Helsinki, Children's Hospital, University of Helsinki and Helsinki University Hospital, Stenbackinkatu 11, PO. Box 281, Helsinki 00029 HUS, Finland
e-mail: mikko.pakarien@hus.fi

T. Wester
Unit of Pediatric Surgery, Karolinska University Hospital and Karolinska Institutet, Q3:03 Solna, Stockholm SE-171 76, Sweden
e-mail: tomas.wester@karolinska.se

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development of bacterial overgrowth following massive distal small bowel resection [6, 8]. Profound unfavorable changes in the intestinal microbiota have been also demonstrated in children with SBS, characterized by overabundance of gram-negative proteobacteria, such as *E. coli*, especially in patients dependent on parenteral nutrition (PN) [9, 10]. Bacterial overgrowth has been reported in up to 60 % of children with SBS mostly after stabilization on parenteral support (PS) with increasing enteral nutrition [11]. Production of D-lactic acid by overabundant gram-positive anaerobes may lead to D-lactic acidosis characterized by anion gap acidosis with low L-lactate and neurological symptoms [1, 2]. Importantly, bacterial overgrowth has potential to further exacerbate malabsorption and promote development of intestinal failure-associated liver disease (IFALD) [9]. Unfavorably altered intestinal microbiota increasingly metabolizes ingested nutrients and deconjugate bile acids, which aggravates lipid malabsorption by reducing micelle formation. Bacterial overgrowth has also potential to cause direct mucosal injury and inflammation, promoting malabsorption and increased epithelial permeability [7, 9]. Epithelial barrier dysfunction may be mechanistically important in the development of IFALD by allowing translocation of certain bacterial species and their antigens into the portal circulation inflicting inflammation-mediated liver injury [9, 12]. Enhanced bacterial modification of bile acid pool has multiple far-reaching effects on health and hepatic function by altering regulative properties of bile acids, which govern their own enterohepatic circulation, as well as lipid and carbohydrate metabolism by ligand activation of specific intestinal receptors.

Normal and uniform bowel diameter can be effectively restored surgically by serial transverse enteroplasty (STEP), while preserving the entire limited intestinal absorptive surface. Elimination of pathological dilatation with simultaneous increase in functional bowel length has potential to decrease PN dependence by improving enteral feeding tolerance and intestinal absorptive function. It is believed that STEP promotes purposeful motility patterns in the dilated small intestinal remnant [1, 13]. Recovery of propulsive motility is expected to reduce bacterial overgrowth [5, 7], while improved mixing of luminal contents and normalization of the bowel width-to-length ratio enhances mucosal contact of nutrients for absorption. Resultant decrease in PS requirement and improved small intestinal mucosal health provides protection against liver injury [14]. Although the exact mechanisms of action remain unclear, some of these assumptions are supported by direct experimental evidence. In pigs with 90 % enterectomy, STEP reduced intestinal overgrowth of gram-negative bacteria (*E. coli*) while improving weight gain and xylose absorption and serum lipid levels [15]. Although STEP animals had higher serum citrulline levels, a surrogate marker of enterocyte mass, no changes in mucosal morphology were observed [15]. One small study in pigs found preserved intestinal motility patterns after STEP when compared to short bowel control animals [15, 16]. In rats, STEP increased weight gain and villus height without change in nutrient absorption [17]. Interestingly, STEP also induced intestinal expression of glucagon-like peptide 2 (GLP-2) receptor and postprandial GLP-2 serum levels. In both pigs and rats, STEP induced longitudinal small intestinal growth [15, 17]. Experimental findings are in line with uncontrolled clinical observations, which demonstrate improving weight gain, stool frequency, and consistency as well as increasing xylose absorption and serum citrulline levels following STEP [18]. The STEP channel does have a tendency for redilatation both in experimental and clinical setting [18], which may compromise functional benefit of the operation in the long term [19].

Indications

Adaptation-associated bowel dilatation often presents clinically with increasing feeding intolerance, which precludes further weaning off PN [1, 20–22]. Other clinical signs are mostly attributable to bacterial overgrowth, including abdominal distension, vomiting, diarrhea, or increased intestinal excretions and D-lactic acidosis [1, 2, 11].

Presence of bowel dilatation is confirmed by intestinal contrast study or MRI enterography in older children. Dilatation may involve only an isolated segment or extend to the entire remaining small intestine. Besides adaptation-associated bowel dilatation, strictures, fistulas, and loss of the ileocecal valve are common predisposing factors to bacterial overgrowth in SBS. Objective preoperative confirmation of small intestinal bacterial overgrowth is more complicated. Diagnostic value and clinical application of hydrogen breath tests is limited especially in neonates with SBS. Traditional cultures of small intestinal aspirates are able to detect alterations only in a fraction of potential microbial pathogens. Modern culture-independent phylogenetic DNA-based microarray analyses have potential to reveal much more detailed intestinal microbiota signatures in children with SBS and clinical diagnosis of bowel dilatation-associated bacterial overgrowth [9].

Indications for STEP surgery are outlined in Table 8.1. The main indication for STEP is persistent PN dependency without further progression of weaning despite optimized nutritional and medical therapy with the presence of excessively dilated remaining small intestine. At this point, most patients display symptoms of intestinal bacterial overgrowth. Patients who continue to progressively wean from PN, despite dilatation, are not candidates for autologous intestinal reconstruction (AIR) surgery. STEP is an effective surgical approach also for neonatal bowel obstruction associated with marginal bowel length that would be further compromised by simple tapering such as intestinal atresia [23]. Small intestinal dilatation has been also pursued intentionally in neonates with congenitally short small intestine by creating temporary controlled bowel obstruction for several months prior to STEP [24].

Table 8.1 Indications for serial transverse enteroplasty

Short bowel syndrome
Unprogressive weaning from parenteral support
Bowel dilatation
Symptomatic intestinal bacterial overgrowth
Diarrhea, increased stromal secretions
Vomiting
D-lactic acidosis
Congenital dilated short bowel
Intestinal atresia
Closing gastroschisis

Patient selection and timing of surgery are essential for successful AIR surgery. STEP surgery should be considered well before progression of IFALD. The presence of jaundice and limited liver fibrosis without concurrent portal hypertension, ascites, or decreased hepatic synthetic function may not decrease postoperative survival [25]. Reversal of IFALD seems to occur in a majority of these patients after successful intestinal lengthening [20, 22, 25–27]. Postponing AIR surgery, if possible, beyond the most efficient period of adaptation taking place during the first year has been considered beneficial by some centers [18, 21, 28]. Theoretically, this could reduce the tendency for adaptation-induced redilatation. Liver failure is a clear contraindication for bowel lengthening procedures. For patients with advanced liver fibrosis and complications of portal hypertension, the primary treatment is intestinal transplantation (ITx) with or without liver component. In general, STEP is contraindicated in primary intestinal motility disorders, because any operative intervention is very likely to further compromise propulsive intestinal motility [29].

Surgical Technique

Kim described STEP procedure experimentally in 2003 and reported the first clinical application later in the same year [30, 31]. After full adhesiolysis the entire remaining intestine is thoroughly evaluated. The operation is performed by firing linear staplers from alternating and opposite directions perpendicular to the long axis of the bowel and parallel to the bowel vasculature (Figs. 8.1a, b). Small openings in the mesentery are created at each point of stapler application. The distance between stapler firings is guided by the pursued bowel diameter, which should be more than 2 cm, depending on age and size of a patient. In addition to restoring bowel diameter,

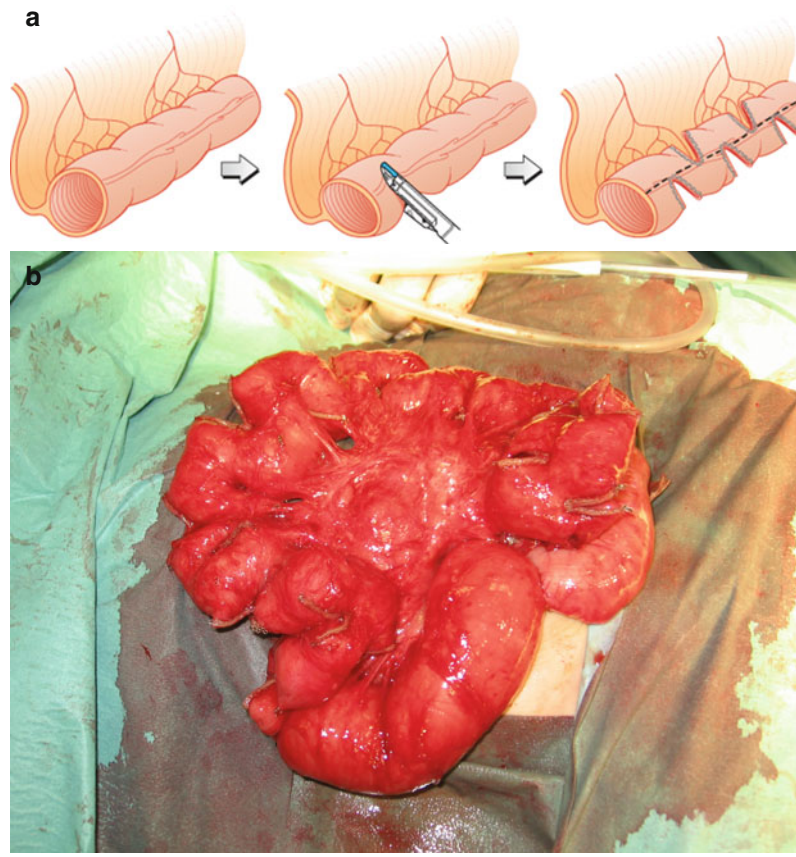

Fig. 8.1 (**a**) In serial transverse enteroplasty, staplers are fired from alternating sides perpendicular to the direction of the bowel (Permission to reprint from John Wiley & Sons Ltd.). (**b**) Photograph showing the small bowel after serial transverse enteroplasty

STEP also lengthens the operated intestinal segment. After STEP, length of the operated bowel segment increases proportionally to the degree of dilatation even more than 100 % [30]. Dilatation of more than 3.5–4 cm is considered the lower limit for efficient bowel lengthening [18, 21, 22, 25, 27]. STEP can be performed and repeated on both symmetrical and asymmetrical bowel, for example, after previous longitudinal intestinal lengthening, and is applicable also in dilated duodenum, which is an important advantage in patients with the shortest jejunal remnants [32]. Other clear technical advances of STEP include limited mesenteric dissection and no need for intestinal anastomoses. STEP procedure may be combined with other autologous reconstructive procedures such as longitudinal lengthening, simple tapering, fistula closures, and alleviation of strictures based on operative findings and individual needs [13, 33].

Complications

Short-Term Complications

Staple-line leaks occur after STEP [18, 34] and may be prevented by placing a stitch at the apex of the staple line. Postoperative bleeding, which requires relaparotomy, are occasionally encountered [22]. The mean incidence of these complications, reported in the publications included in a systematic review, was 12 and 22 %, respectively [35]. Obstruction has been reported to occur in 17.5 % of the patients [35]. Obstructive symptoms are usually caused by prolonged postoperative ileus, which eventually resolves without operative intervention. It has recently been shown that 16–35 % of patients undergoing STEP get catheter-related blood stream infections during the first few weeks after the procedure [21, 36].

Long-Term Complications

Infectious complications are common long-term complications after STEP. One study showed that 10 of 12 patients had experienced at least one episode of septicemia with positive blood cultures after STEP [22]. Post-STEP blood stream infections may originate either from central venous catheter or from the intestine by translocation.

Chronic gastrointestinal bleeding due to staple-line ulcers is another well-described long-term complication [34, 37–39]. In patients with anemia and occult gastrointestinal bleeding, endoscopy or video capsule imaging can be used to reveal ulcerations at staple sites [39]. The ulcers may have to be resected in recalcitrant cases. Push enteroscopy is useful to identify the ulcers intraoperatively [34]. The etiology of chronic ulcers is not clear [18]. Recently, it was shown in a pig model that STEP could be accomplished safely with application of a sealing device (LigaSure™; Covidien, Dublin, Ireland) instead of using conventional staplers [40]. This may potentially prevent bleeding complications from staple-line ulcers.

Dilatation of the small bowel is part of the adaptation process in SBS [1]. It has been reported that redilatation of the small intestine occurs in 30–67 % of the patients after STEP, usually during the first postoperative year [35]. Redilatation has been considered an indicator for poor outcome after AIR [41]. One single-center report showed that 9 of 16 patients developed moderate to severe dilatation after STEP. The only factor, which was associated with redilatation, was the duration of PS after STEP [42]. There are patients who have recurrent dilatation, which does not affect their bowel function. However, many patients have symptoms of deteriorating enteral tolerance, bacterial overgrowth, and need for enteral antimicrobial therapy. Most of these patients benefit from a repeat STEP procedure [43].

Redo Step

In 2006, it was shown that redo STEP was feasible in a pig model [43]. Redo STEP was first described in humans in 2007 [44]. Fourteen of 111 patients reported in the STEP Data Registry underwent a redo STEP [45]. Redo STEP can be performed after STEP but is also an option for redilatation after LILT [46]. The indications and surgical technique for redo STEP are similar to those for the primary procedure. Usually, the stapler is applied between the staple lines of the first STEP. One consequence of redo STEP may be that blind-ending, redundant, small bowel tags are formed. These can predispose for bacterial overgrowth that should be removed with a tapering enteroplasty [44].

Outcomes

In a porcine model of short bowel syndrome, it was shown that STEP prevents weight loss and improves nutritional status, intestinal absorptive capacity, and serum citrulline levels [15]. Also in humans, it has been shown that serum citrulline levels increase after STEP, possibly indicating an increased small bowel mucosal enterocyte mass [34]. D-xylose absorption increases after STEP [18]. It has been shown that serum bilirubin, aspartate aminotransferase, and alanine aminotransferase levels improve after STEP along with increasing enteral tolerance [22].

Nutritional Outcomes

The mean proportion of patients weaned off PN after STEP was 58 % in the publications included in a recent systematic review [35]. The mean time to weaning off PN was 9 months [35]. Enteral autonomy was achieved in 33–88 % of the patients included in the studies summarized in Table 8.2 [18, 21, 22, 28, 34, 37, 38, 45, 47]. It is obvious that children with intestinal failure and treatment strategies are quite heterogeneous, which may contribute to the variation between centers. Longer pre-STEP bowel length is independently associated with attainment of enteral autonomy after STEP [40]. The effect of STEP on growth varies between different reports. One study showed that only z-scores for age-adjusted height improved significantly [22]. Another

Table 8.2 Outcomes after STEP

Reference	Year	Study location	*n*	Follow-up	Total small bowel length gain (%)	Enteral autonomy (%)	Small bowel transplantation (*n*)	Death (*n*)
Jones et al. [45]	2013	International STEP Data Registry	97[a]	Median 21 months	53	47	5	11
Wales et al. [34]	2007	Toronto	14	Mean 23 months	49	88	2	3
Ching et al. [37]	2009	Boston	16	Median 23 months	91	38	2	0
Oliveira et al. [18]	2012	Toronto	12	>5 years	46	88	2	2
Pakarinen et al. [28]	2013	Helsinki	7	Median 6.9 years	43	86	0	1
Javid et al. [38]	2013	Seattle	16	Median 26 months	38	60	2	2
Wester et al. [22]	2014	Sweden	12	Median 37.2 months	48	58	0	0
Mercer et al. [21]	2014	Omaha	51	Median 39 months	54	60	7	3
Oh et al. [47]	2014	New York	15	Median 6.5 months	42	33	1	0

STEP serial transverse enteroplasty
[a]A total of 111 patients were included in the registry, but there were adequate data for analysis on only 97

showed that only weight for age improved after STEP [21]. In one study, both height for age and weight for age z-scores improved [34]. Approximately half of the patients can be weaned off PN after redo STEP [22, 46]. Catch-up growth has been shown to occur also after redo STEP in children [46].

Small Bowel Transplantation and Mortality

In most series of STEP patients, mortality or ITx have been relatively rare events (Table 8.2). The indication for ITx is often progressive liver failure. Mortality is frequently related to liver failure or serious infections, sometimes after ITx. STEP and redo STEP do not preclude later ITx if the procedures are unsuccessful. The patients in the STEP Data Registry were divided in two groups: transplant-free survivors ($n=81$) and those who underwent ITx or died ($n=16$). There was no statistical difference between the two groups with respect to sex, ethnicity, gestational age, diagnosis, weight at STEP, or presence of ileocecal valve. However, shorter small bowel length and higher serum bilirubin concentrations before STEP were independently associated with death or ITx after the first STEP [39]. Elevated conjugated serum bilirubin has previously been shown to be a very significant negative predictor of survival in children with SBS [48].

Conclusion

In children with intestinal failure and symptomatic bowel dilatation, accompanied with unprogressive weaning from parenteral nutrition, STEP has the ability to increase enteral tolerance and limit symptoms of bacterial overgrowth. However, a significant number of patients develop recurrent dilatation, requiring repeated STEP. The complication rate is low, but sometimes STEP alone is insufficient to fully control bacterial overgrowth. In the future, additional modalities, combined with STEP, may improve the efficacy of the procedure and the outcomes.

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Longitudinal Intestinal Lengthening

9

Lucas Marie Wessel and Rasul Khasanov

Abbreviations

BaFT	Barium follow-through
ICV	Ileocecal valve
IFALD	Intestinal failure-associated liver disease
LILT	Longitudinal intestinal lengthening and tailoring
PDC	Peridural catheter
PN	Parenteral nutrition
PNALD	Intestinal failure-associated liver disease
SBS	Short bowel syndrome
SBTx	Small bowel transplantation
STEP	Serial transverse enteroplasty

L.M. Wessel (✉)
Pediatric Surgery Department, University Hospital Mannheim, University of Heidelberg, Mannheim, Germany
e-mail: lucas.wessel@medma.uni-heidelberg.de

R. Khasanov
Pediatric Surgery Department, University Hospital Mannheim, University of Heidelberg, Mannheim, Germany

Pediatric Surgery Department, Bashkir State Medical University, Ufa, Russia

Definition and History

Longitudinal intestinal lengthening is a method of surgical treatment of a short bowel syndrome when dilated small bowel is lengthened and tailored during surgical reconstruction. Diminished diameter of the small intestine results in a better motility of the bowel as well as a lesser extent of bacterial overgrowth and translocation from the bowel. So reduction of small bowel diameter, achieved with preservation of surface area of intestinal mucosa, is more important than extension of its length [1]. Removal of pathological dilatation retrieves normalization of propulsive motility, which is accomplished with favorable effect on bacterial overgrowth and intestinal function. Adjustment of the bowel to physiological width/length ratio intensifies contact between mucosa and essential nutrients and absorption [2].

In 1980 Bianchi introduced a small bowel longitudinal intestinal lengthening technique in a pig model, and this technique was named longitudinal intestinal lengthening and tailoring (LILT) [3]. Boeckman and Traylor [4] initiated this technique in clinical practice. Their first patient was a 4-year-old child on parenteral nutrition with a 50-cm jejunum. The operation resulted in an ability to wean off parenteral nutrition (PN) after 10 weeks [5]. LILT is the first developed small bowel lengthening procedure. Since its first application, this procedure is widely adopted [6]. Significant studies showed efficiency of LILT in

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short bowel syndrome [7–10]. Nowadays the experience of such surgical treatment is the largest comparing to other lengthening techniques around the world [6, 11].

The objectives of lengthening procedures are avoidance of bacterial translocation and sepsis, bacterial overgrowth, and increasing dystrophy, prolongation of transit time, and optimization of resorption of fluids and nutrients in order to gain intestinal autonomy (Table 9.1).

Table 9.1 Objectives of lengthening procedures

Avoidance of bacterial translocation leading to sepsis
Avoidance of bacterial overgrowth
Prolongation of transit time and optimization of resorption of fluids and nutrients
Gaining intestinal autonomy

Principals and Justification

LILT technique is based on anatomical peculiarity of blood supply of the small intestine, where two leaves of the mesentery provide blood supply to each half of the circumference of the small bowel (Fig. 9.1a). Therefore, the small bowel can be divided longitudinally in the midline along the mesenteric and antimesenteric borders in order to create two sufficiently vascularized narrowed tubes which are implanted end to end in continuity of the bowel [5, 12]. This method does not change the physiological direction of longitudinal and circular muscle layers, which could play a beneficial role in intestinal function afterward [13].

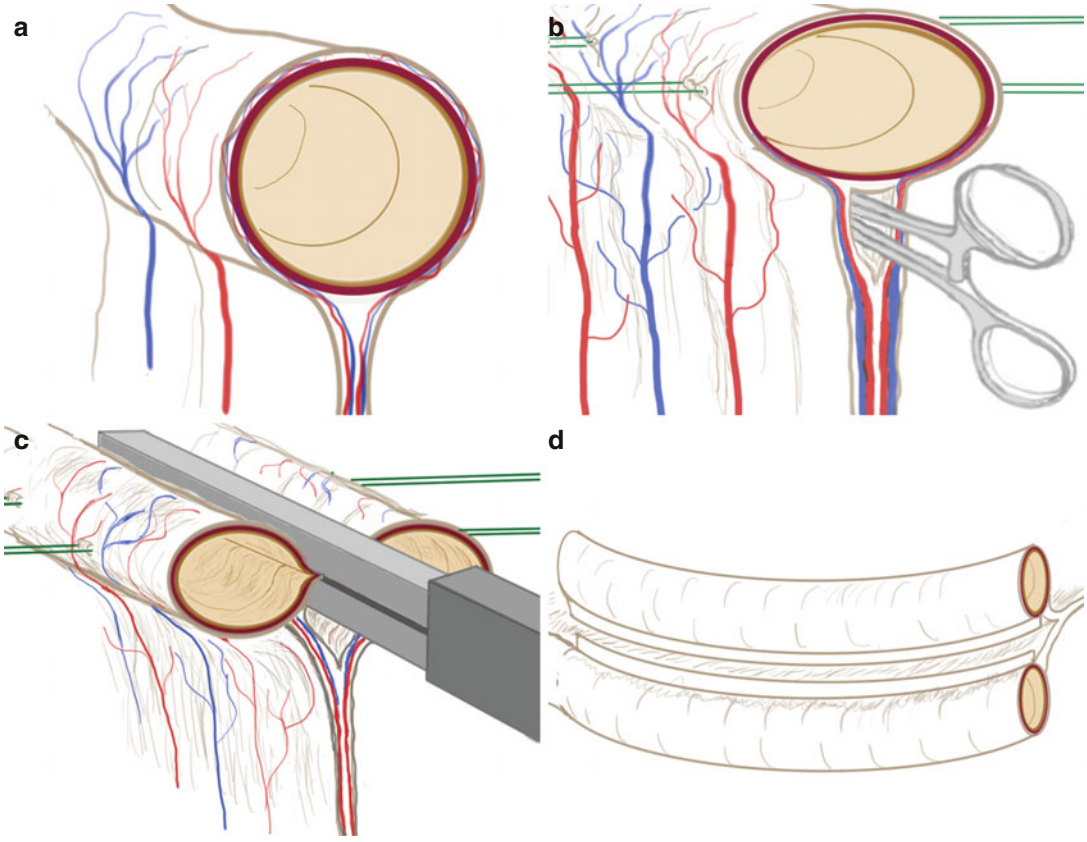

Fig. 9.1 Longitudinal intestinal lengthening and tailoring: main steps of the surgery. (**a**) Dilated small bowel: two leaves of the mesentery provide blood supply to each half of the circumference of the small bowel. (**b**) Separation of the mesentery vessels to the left and right side with forceps according to their belonging to right or left mesenteric leaf. (**c**) The stapler divides the bowel into two loops. (**d**) Two newly formed small intestine loops

Indications and Contraindications

The selection of patients and the timing of operation are very important for achievement of good results. Lengthening procedures can be performed only in patients with short bowel syndrome, so accurate differential diagnosis with chronic intestinal pseudo-obstruction is necessary.

Indications for operation are dependent on parenteral nutrition and impossibility of achieving at least 50 % of the caloric requirement enterally, after 6 months of adequate conservative treatment [8].

Because of technical peculiarities, LILT can be performed only on dilated small bowel (Fig. 9.2a). In order to make longitudinal dissection of the bowel possible, diameter of dilated bowel must be twice as large as normal small bowel or more but not less than 5 cm, and it must be symmetrical. The dilated segment of the small bowel should be longer than 20 cm. Such length is necessary to avoid volvulus of created bowel loops after its anastomosation. It is possible to perform LILT procedure only in bowel that has a mesentery; consequently, it is not applicable on the duodenum.

The first year of life is not a suitable time for lengthening procedures. At this time, small bowel has a large potential for spontaneous growth and intestinal adaptation. Presence of ileum, ileocecal valve (ICV), and colon intensifies intestinal adaptation. It is known that the adaptive potential of ileum is greater than of jejunum. Ileal enteroendocrine L cells

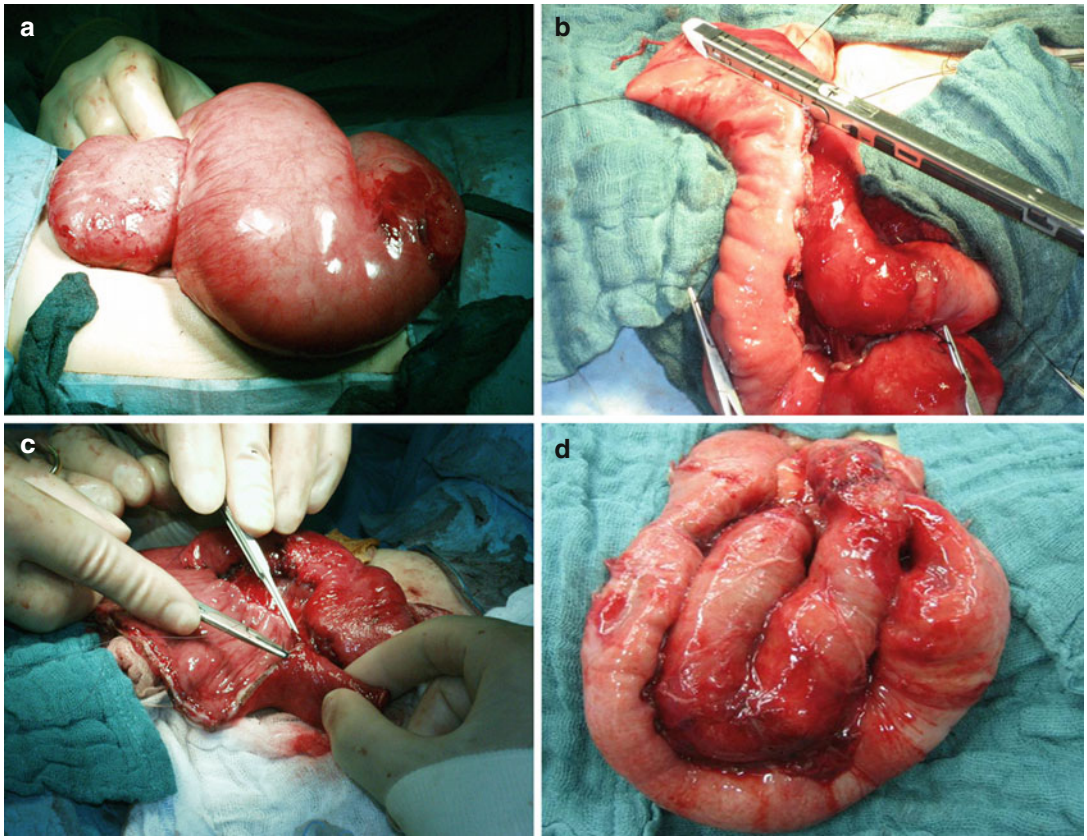

Fig. 9.2 Photographies from surgery. (**a**) Dilated small bowel in child with a short bowel syndrome. (**b**) The stapler divides the bowel into two loops. (**c**) New loops are formed with inverting running sutures. (**d**) Anastomosed small bowel loops after LILT, the construction comes out as a spiral-formed part of the bowel

produce peptide YY, glucagon-like peptide-1, and glucagon-like peptide-2 (GLP-2) [2, 14, 15], which influence on histology and function of the gut. Peptide YY and glucagon-like peptide-1 effect gastric emptying and intestinal transit. Glucagon-like peptide-2 acts as intestinotrophic peptide stimulating mucosal growth and could be associated with mucosal hypertrophy [2, 15, 16]. The administration of GLP-2 improves clinical, functional, morphological, and histological outcomes [17, 18]. The ICV is a strong predictor of weaning off PN at the time of diagnosis; however, it is believed that the role of the ICV in achieving enteral autonomy may be actually mediated by the residual terminal ileum, which is always retained together with an intact ICV [19]. The colon in SBS in addition to its physiological abilities increases intestinal energy salvage by metabolizing carbohydrates to short-chain fatty acids, which are effectively absorbed in the colon [2, 20].

Surgery during first year of life can harm potential for intestinal adaptation. Therefore, the indications for surgery during the first year should be very restricted. Exception could be done for progressive small bowel dilatation with aggressive bacterial overgrowth, which cannot be treated by conservative methods and leads to repeated life-threatening episodes of sepsis. In such cases, lengthening procedures may have positive effect against bacterial overgrowth and translocation.

For example, in a patient P (gestation age, 32 weeks; birth weight, 1400 g) with gastroschisis due to necrosis, a resection of large part of small bowel and half of the colon with ileocecal valve was necessary. In spite of intensive conservative treatment and several repeated surgeries to correct relapsing stenosis, the condition of the patient deteriorated. He developed functional ileus, recurrently bacterial overgrowth and translocation, chronic *Cytomegalovirus* infection, and cholestatic hepatopathy. Therefore, adequate parenteral as well as enteral nutrition was not possible to provide and to assure thriving. At the age of 8 months, the patient underwent LILT. His jejunum, dilated to 8 cm, was tailored in half of previous bowel diameter and lengthened from 50 to 100 cm. Afterward, the condition of the patient improved. In a follow-up control 6 months after LILT, the child was in a good general condition and on partly parenteral nutrition. His weight increased to 8770 g. In a year after LILT, the patient weaned off PN.

Intestinal failure-associated liver disease/parenteral nutrition-associated liver disease (IFALD/PNALD) in severe stage such as hepatic fibrosis or liver failure may be contraindication for lengthening procedures. Hepatopathy manifests itself as liver insufficiency and impairs blood coagulation, which leads to severe complications during surgery as well as during postoperative period, which increases postoperative morbidity and mortality [7]. However, there is data showing that LILT procedure can improve damaged hepatic function [21, 22]. SBS patients usually have many adhesions in abdominal cavity, which might cause severe bleeding during this surgery. Therefore, impaired coagulation may be an important contraindication for LILT surgery as far as substitution of clotting factors is not possible.

LILT is a complicated and challenging operation, which requires enough condition from the patient to endure surgery and postoperative period. Thus, distinct cachexia is also contraindication for LILT. Before indicating LILT the cachexia should be treated by PN.

The patients with SBS require parenteral nutrition and intravenous correction of electrolytes. In early postoperative period after LILT, the necessity of parenteral nutrition increases considerably. In order to keep control of the patient's alimentation, LILT surgery can be performed only in patients who have central line blood catheter (*Broviac*, *Hickman*). Otherwise, a central line should be implanted at the beginning of the operation.

For patients with severe stage of IFALD/PNALD and/or without possibility to place a central line (*Broviac*, *Hickman*), small bowel transplantation (SBTx) should be considered.

Indications and contraindications for lengthening procedure are assembled in Table 9.2.

Preoperative Management

The LILT surgery can be performed only on dilated bowel; for this reason, the state of the bowel should be carefully evaluated. Ultrasonography of the abdomen and contrast agent barium follow-through (BaFT) investigations should be done to consider condition of the small bowel, diameter, length, and dilatation. Magnetic resonance imaging gives comprehensive information about small bowel anatomy. Ultrasonography should be used for examination of the liver for IFALD (portal blood flow and pressure) and kidneys for nephrocalcinosis. These conditions indicate imbalance of parenteral nutrition. The LILT surgery should not be performed in patients with acute episode of sepsis or infections.

Preoperative examination should contain physical status and blood tests: blood cell count, serum electrolytes, C-reactive protein, transaminases, bilirubin, acetylcholinesterase, total protein and albumin, fat-soluble vitamins, trace elements, and coagulation tests [8]. Hypoalbuminemia and hypoproteinemia should be corrected by adjustment energy and amino acids supply in PN. If there is a lack of coagulation factors, these factors should be substituted. It is necessary to compensate nutritional deficits such as deficits of vitamins (vitamin B12, fat-soluble vitamins such as vitamin K, which are important for synthesis of coagulation factors) and trace elements and also to correct electrolyte and acid–base disorders, anemia, coagulation disorders, and thrombocytopenia. It is also highly important to detect and treat thrombosis resulting from the central venous catheter [8]. In order to prevent thrombosis in postoperative period, adjustment of coagulation parameters must be taken into account.

During the surgery, considerable blood loss must be anticipated; therefore, blood components for transfusion should be prepared.

Table 9.2 Indications and contraindications for lengthening procedure

Indications	Contraindications
Dependence on parenteral nutrition	Distinct cachexia
Massive dilation (bacterial overgrowth)	Chronic intestinal pseudo-obstruction
Doubled diameter of small bowel, but not less than 5 cm	Progressed liver disease and impaired coagulation (IFALD; PNALD)
Length of dilated small bowel more than 20 cm	No possibility to insert central line (Broviac, Hickman)
Need to eliminate reservoir for bacterial overgrowth and translocation: stenosis, fistula, blind loops	No dilation of small bowel
Need to eliminate obstructions (beware of supposed stenosis)	

Surgery

The patient is placed in the supine position. The large midline or transverse incision is made. Present incisions should be used again. Due to massive adhesions, which can be definitely found in patients with short bowel syndrome, care must be taken in order not to injure hollow viscus or solid organs during opening of peritoneal cavity. All adhesions should be gently removed. During adhesiolysis, there is a risk of multiple bleeding, which may require transfusion of blood components (erythrocyte, thrombocyte, plasma). The small bowel from the duodenum until the colon should be mobilized. The length of the whole small bowel as well as length and width of dilated segment should be measured on antimesenteric side without stretching the intestine. At the point where dilated segment ends, the small bowel is transected transversely, and bowel lumen is sanitized. Then stay sutures are placed on dilated segment in the middle between mesenteric and antimesenteric parts from both sides (each 2–3 cm). These stay sutures are used to obtain essential tissue tension and to manipulate the bowel. At the mesentery a wide triangle containing vessels is found where preparation should begin. The next step is a careful separation of the mesentery vessels to the left and right side with scissors or forceps according to their belonging to the right or the left mesenteric leaf (Fig. 9.1b). As a result, a mesenteric tunnel is created, which

should be large enough to introduce GIA stapler. Due to its smaller size in children, the use of Endo GIA is recommended. The smaller branch of the stapler is put in the tunnel; the thicker branch is placed on antimesenteric side of the bowel accurately in the middle (Fig. 9.1c). The stapler divides the bowel into two loops. This step must be repeated several times, until the whole dilated bowel is dissected (Fig. 9.2b). It is very important not to twist the small bowel during the dividing procedure in order to prevent torsion of the vessels.

If mesenteric tunnel is too narrow to use a stapler, the sharp longitudinal division can be performed surgically. In this approach, the bowel is transected longitudinally with scissors, needle-tip electrocautery, or bipolar scissors along the antimesenteric and mesenteric borders. New loops are formed with inverting running sutures [7, 8] (Fig. 9.2c). This procedure is longer lasting, and risk of anastomotic insufficiency is greater than in using stapler.

One of received loops is cut off from continuity of the bowel (Fig. 9.1d) and anastomosed isoperistaltically to the second received loop and helically to the distal part of the bowel. This construction comes out as a spiral-shaped part of the bowel (Fig. 9.2d). As a result, dilated part of the bowel is tapered to half of the initial diameter, and its length is twice as long as its previous size.

It is important to include all intestinal segments into bowel continuity in order to recruit the entire resorption area of the intestine.

The patient should receive a peridural catheter (PDC) by anesthesiology team for postoperative analgesia and to ameliorate postoperative motility.

Postoperative Management

After completion of the surgery the patient is transferred to an intensive care unit usually for 2–3 days. Postoperative pain control with PDC generally lasts for about 4–5 days. Two antibiotics are administrated for 1–2 weeks after surgery or longer, if necessary. In the early postoperative period, an oral gastric tube is left in place until bowel function returns. During the first days, the patient receives total parenteral nutrition (TPN). Oral feeding starts slowly only after restoring motility of small bowel, when gastric reflux reduces, usually on the fifth postoperative day. Feeding should be advanced very carefully and slowly. The management of these patients requires a multidisciplinary team, including pediatric surgeons, intensivists, neonatologists, pediatricians, and gastroenterologists. Multidisciplinary intestinal rehabilitation programs are associated with reduced morbidity and mortality [23].

Outcome

At the average LILT can increase overall intestinal lengthening to 48 % (25–100 %) of bowel's length [6]. In our experience with LILT, the main small bowel length increased to 52.9–55.9 % [8, 24].

Weaning Off Parenteral Support Achievement of enteral autonomy through weaning off parenteral nutrition (PN) is the principal aim of the LILT. The first significant data about weaning off PN were published by Bianchi in 1997. The author reported achievement of full enteral nutrition in seven out of the nine (77.8 %) surviving patients within 8–16 weeks from LILT procedure [25]. Two years later, Waag et al. described getting of enteral autonomy in 17 out of 18 (94.4 %) patients within the period from 1 to 10 months [7]. The same year Weber T.R. reported that 14 out of 16 (87.5 %) surviving patients at 12 months postoperatively were receiving their nutrition all enterally [26]. In 2012, Khalil et al. published data where 13 out of 15 (86.6 %) patients after LILT, who survived and are not lost to follow-up, weaned off from total parenteral nutrition [10]. However, there are articles with low weaning off PN rate; for example, only 8 from 19 (42 %) patients weaned off PN after LILT [27]. In a systematic review of Frongia et al. in 2013, it is shown that in about 10.3 months (5–21 months) after LILT, 71.5 % (4–100 %) of patients could wean off PN [6]. Meanwhile in a systematic review from King B. et al., it was shown that enteral autonomy could be achieved in 54.9 % of

patients [11]. In our clinic, successful weaning off PN was defined as 4 weeks weaning off PN period without weight loss [24]. Our experience showed that 36 out of 41 (87.8 %) surviving patients could successfully wean off PN. In a long-term follow-up, 79 % stayed free of PN [8, 24]. It is important to evaluate not only weaning off PN ratio but also the ability of the patients to stay free of PN in a follow-up.

Mortality The data about survival in patients after LILT procedure is very diverse indeed. Bianchi showed in his review article in 2006 an overall survival ranging from 30 to 100 % [22]. The mortality after LILT significantly changed as time went by. In 1997, the mortality rate after LILT was 55 % (11 out of 20 patients) in a mean follow-up period of 6.4 years (range 0.5–15) [25]. However, no surgery-related mortality was described. The main reason for mortality was hepatic failure in ten patients and sepsis in one patient. In contrast, in further publication of the same group from 2012, the mortality rate did considerably ameliorate. Overall mortality was only in 2 out of 27 (8 %) patients encountered [10]. Systematic review from King B. et al. showed 19 % mortality rate after LILT [11]. At the same time, the systematic review from Frongia et al. showed that the main postoperative mortality rate is 30.2 % in LILT cases [6]. In our hands, LILT is a safe therapy. There was no mortality as direct consequence of the procedure in our institution [7, 8]. In our series the overall mortality rate was 22.6 %. The most frequent reasons for death were liver failure in four patients, sepsis (central venous line) in three patients, and pneumonia due to gastroesophageal reflux disease (GERD) in two patients [24]. All patients who did not survive died within the first 22 months after LILT [24]. The postoperative mortality rate after LILT depends mostly not on the operation itself but on the underlying compilations of SBS, preoperative selection of patients, and development of nonsurgical methods of SBS treatment.

Complications Possible complications of LILT are ischemia of a part of short bowel segment, leakage of suture, formation of abscesses [8], small bowel stenosis, and/or intestinal fistula with formation of a blind intestinal loop. By other authors, bleeding, intestinal necrosis, and perforation have also been described [6], which we did not face in our series. Among them, the most challenging complication is recurrent and recalcitrant bacterial overgrowth, which impairs considerable malabsorption and requires intensification of TPN. These problems can be treated with conservative and operative methods.

Redilation Intestinal redilation gives a signal that the bowel returns to a dysfunctional state [28]. It is an important outcome-influenced complication of LILT [7], which impairs intestinal transit, promotes bacterial overgrowth, and thereby intensifies malabsorption by SBS patients. It is shown that patients with intestinal redilation have lower weaning from PN rate comparing with patients after LILT without redilation. The reoperation frequency by patients with redilation was significantly higher as well [28]. In systematic review from 2013, Frongia et al. reported about 39 % of redilation rate after LILT [6]. Miyasaka et al. reported that in their series, four out of seven (57 %) patients developed intestinal redilation. In our series recurrent dilation of the lengthened bowel segments was the most frequent complication in the long-term follow-up. This condition manifests itself as dysmotility, stasis, and bacterial overgrowth which leads to steatorrhea, D-lactic acidosis, cholelithiasis, urolithiasis, and malabsorption [8]. Symptomatically, these symptoms can be treated with dietary measures and bowel decontamination with cyclic nonabsorbable antibiotics. However, success of antibiotic decontamination is not very consistent. Surgically intestinal redilation may be treated with serial transverse enteroplasty (STEP) according to Kim et al. [24, 29].

Predictive Factors for Successful Outcome Predictive factors for successful outcome in patients with SBS can be divided into two groups: general factors and surgery-related factors.

General factors for successful outcome are residual bowel length >35 cm or ≥10 % of

age-expected length, older infant/child at initial bowel loss, jejunal resection, presence of terminal ileum/ileocecal valve, presence of colon, earlier reestablishment of bowel continuity, and necrotizing enterocolitis (NEC) and intestinal atresia as underlying causes of bowel loss [19, 30]. Factors associated with worse outcomes are primary intestinal motility disorders or enteropathies, residual bowel length <20 cm or <10 % of age-expected length, end jejunostomy, less than 40 cm of small bowel with partly preserved colon without ileocecal valve, less than 15 cm of small bowel with ileocecal valve and entire colon, full-term or beyond at-time intestinal resection, prematurity/younger infant at initial bowel loss, ileal resection, IFALD/PNALD, bacterial overgrowth, gastroschisis as underlying cause of bowel loss, and recurrent catheter-associated infections [2, 30]. In our view the worst survival prognosis have patients who own only small part of jejunum, without ileum, ileocecal valve and have less than 30% of the colon as well as intestinal neurodegenerative pathology (Zuelzer–Wilson syndrome). These patients have severe malabsorption, reduced intestinal adaptation potential, and high complication rate (IFALD/PNALD, recalcitrant bacterial overgrowth, sepsis, etc.).

Besides general factors, surgery-related factors are also important for successful outcome in patients with SBS. IFALD/PNALD is a very challenging issue. All patients with end-stage liver disease died of liver failure in the early postoperative period that is why such patients should be treated for liver insufficiency or be considered for small bowel or multi-organ transplantation. Furthermore, surgical therapy should be performed as soon as it was indicated because prolongation of an unsuccessful conservative treatment increases risk of worsening liver function and developing other major complications [8]. The length of the colon, especially the remaining right hemicolon, has a significant impact on the survival. ICV is a strong predictor of weaning off PN but only during the first year of SBS; after 1 year of PN dependence, ICV influences the outcome not significantly [19]. LILT is usually performed in selected cohort of patients, who are already depending on PN for some time. For such patients presence of the ileocecal valve did not influence the prognosis [24]. Small bowel length is important regaining achievement of intestinal autonomy [2]. The shortest small intestinal remnant is a negative prognostic factor [31]. Apart from extremely short segments, preoperative bowel length in patients who required LILT had no statistically significant influence on outcome [24]. Duration of PN is a significant prognostic parameter after LILT. The patients who exceeded 18 months of PN showed a significantly worse prognosis for survival [24].

Longitudinal Intestinal Lengthening and Tailoring (LILT) and Serial Transverse Enteroplasty (STEP) LILT and STEP are autologous gastrointestinal reconstructive procedures, which can be performed only on dilated small intestine. In spite of that, surgical techniques of these methods are different; the object of both approaches is to return the bowel lumen diameter to normal size without loss of adapted valuable bowel mucosa and restoration of affected intestinal transit [5]. Both techniques reduce stasis and bacterial overgrowth, facilitate food contact with bowel mucosa, and improve nutrient absorption [5]. The comparison of LILT and STEP shows advantages of each method in certain aspects; however, the results depend on many factors [6, 11]. The single center comparison study also showed some distinctions between LILT and STEP, but could not find significant differences in terms of survival, PN weaning, and complications [29]. The experience of STEP shows that it is a useful procedure for selected patients with SBS and seems to facilitate weaning off PN [32]. In our view LILT and STEP both are efficient methods; each of these has specific indications and limitations. The main advantages of LILT include maintaining of physiological direction of longitudinal and circular muscle layers after procedure [13] and delayed bacterial overgrowth in comparison with STEP. The main disadvantages of the LILT are its technical difficulty, the need for the dilated segment of intestine to be symmetrically dilated, and it can only be performed once [30].

Dynamics of Body Weight and Conclusion Fifty-eight percent of the patients gained weight to a higher percentile after LILT [24]. However, most of the patients remain between 2nd and 5th percentiles, lower than average value. Almost all patients after LILT need a special diet or have a tendency to diarrhea. Only 10 % of the patients report severe reduced physical conditions [24].

LILT is a safe surgical method, which effectively counteracts bacterial overgrowth, increases intestinal absorption, weans SBS patients from PN, and improves quality of their life.

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Controlled Tissue Expansion

10

Riccardo Coletta and Antonino Morabito

Abbreviations

CTE	Controlled tissue expansion
NG	Nasogastric tube

Introduction

The idea of expanding bowel to create enough tissue in preparation for a lengthening procedure was introduced by Georgeson et al. in 1994 [1]. The authors described a nipple valve to occlude bowel's lumen. This process by creating a noncontrolled bowel obstruction generates intestinal dilatation [2].

Bianchi introduced the concept of controlled tissue expansion (CTE) modifying the nipple valve idea of Georgeson [3] and proposed this approach serially within the intestinal rehabilitation programme held in Manchester [4]. The CTE allows controlled expansion of the bowel as the occlusion of the bowel lumen is monitored and controlled from outside the intestinal lumen minimising the risk of bacterial overgrowth and translocation. The discomfort and pain are therefore minimal as the clamping can be stopped at any time. Controlled tissue expansion allows bowel dilatation in 20/24 weeks.

In this chapter, we aim to describe clearly the indication, surgical technique, protocol and troubleshooting in the use of CTE clamping–recycling programme.

Preoperative Assessment of SBS Patient Before Controlled Tissue Expansion

Short bowel is usually secondary to an intra-abdominal catastrophe [5]. Once the diagnosis of short bowel has been placed and the patient is stable under general anaesthesia, the decision to create a stoma for clamping–recycling should follow. The procedure is straightforward and takes less time than a formation of stoma, moreover allows saving a few centimetres of bowel, which is essential in the short bowel patient.

The premature patients require careful evaluation. The diagnosis of short bowel should not be made in a premature baby as the bowel has the ability to physiologically grow in the last trimester of

R. Coletta, MD
Paediatric Autologous Bowel Reconstruction and Rehabilitation Unit, Royal Manchester Children's Hospital, Manchester, UK

Institute of Human Development, Faculty of Medical and Human Sciences, University of Manchester, Manchester, UK

School of Environment and Life Sciences - University of Salford, Manchester, UK

A. Morabito, MD (✉)
University of Manchester and Royal Manchester Children's Hospital, Manchester, UK
e-mail: antonino.morabito@cmft.nhs.uk

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pregnancy; therefore, a natural elongation of bowel is to be expected in this group of patients [6].

We use the CTE in term neonates with remaining bowel of 30 cm or less in order to maximise the potential of bowel adaptation. In our experience, the creation of tube stomas at the time of diagnosis helps in avoiding delays in the treatment and reducing the number of surgeries and bowel loss. It is also important to note that the clamping–recycling works better in the neonatal phase, as the procedure is better tolerated and easier to deliver. The older child due to dietary requirements finds the clamping–recycling uncomfortable.

In the presence of an acute abdominal problem in an older child, the possibility of restoring bowel continuity (and wait for natural dilatation of the bowel) can be an option due to the more difficult implementation of the clamping–recycling stomas in this group of patients.

In our experience, older children are more difficult to manage with the clamping–recycling stoma due to lack of compliance.

Operative Technique

The idea to expand the intestine in a controlled way has been adopted from Georgeson's idea to distend bowel by creating a nipple valve [1].

In a term baby, immediately at first surgery after an intra-abdominal catastrophe, a silicone Malecot catheter (usually a size 12–14Fr) or a Foley catheter (usually a size 8–10Fr) is introduced into the obstructed end of the dilated jejunum and is brought out onto the abdominal wall as a tube jejunostomy/ileostomy (tube stoma). A second tube is positioned into the lumen of the distal bowel and brought out onto the abdominal wall as a tube ileostomy/colostomy (Fig. 10.1a).

Tightening a purse string suture on the bowel wall around the tube and securing it to the abdominal wall create both tube stomas. We suggest labelling both proximal and distal tubes to avoid error and to help family care of the tubes. Finally both tubes are secured to the skin using a stabilisation dressing to prevent accidental removal of the tubes [7] (Fig. 10.1b).

Using this approach, surgery appears to be minimal, and no bowel is lost or sacrificed.

Controlled Tissue Expansion Clamping: Recycling Approach

Occlusion of the tube jejunostomy for variable periods induces controlled bowel expansion. Bowel expansion has the added advantage of inducing new mucosal growth, thereby creating new mucosal surface area for absorption.

Collected intestinal contents are recycled down the distal tube stoma at a slow steady rate to stimulate mucosal absorption and adaptation in the distal bowel also. This model allows direct access to the jejunum for several procedures such as bacterial cultures, loop washouts, endoscopy and biopsy.

CTE clamping–recycling is maintained for several months until sufficient dilatation has been achieved, and the child is generally fit for lengthening procedures. We advise to perform CTE clamping–recycling for a period of 22–24 weeks and to perform a preoperative contrast study measuring intestinal dilatation.

In our unit, the child is preferably orally fed and if that is not possible via gastrostomy/nasogastric tube (NG). At the time of feeding, the proximal catheter is clamped for a period of time (routinely starting at 5 min and increased by 5 min/day). The gastrostomy/NG (if present) also is clamped.

In the CTE clamping–recycling at the end of the clamping period, the proximal output is collected until the drainage stops (usually 15–20 min). The effluent is then immediately recycled through the distal tube stoma over a period of 45 min maximum to prevent bacterial overgrowth. We advocate recycling a maximum of 150 ml of intestinal content because high volume will not be tolerated and the patient may develop diarrhoea. We recommend performing the recycling using a slow infusion rate by pump or using a syringe by gentle injection. We also suggest not recycling the content as a bolus, thus avoiding diarrhoea. All the intestinal content exceeding the 150 ml mark will be discarded [8].

Regular washout of the proximal stoma with saline helps preventing bacterial overgrowth. The goal is to get the child to full complement of feeds at 3–4-h intervals with the clamp on throughout the interval period.

Monitoring during the CTE clamping–recycling is mandatory to reduce the risk of complications.

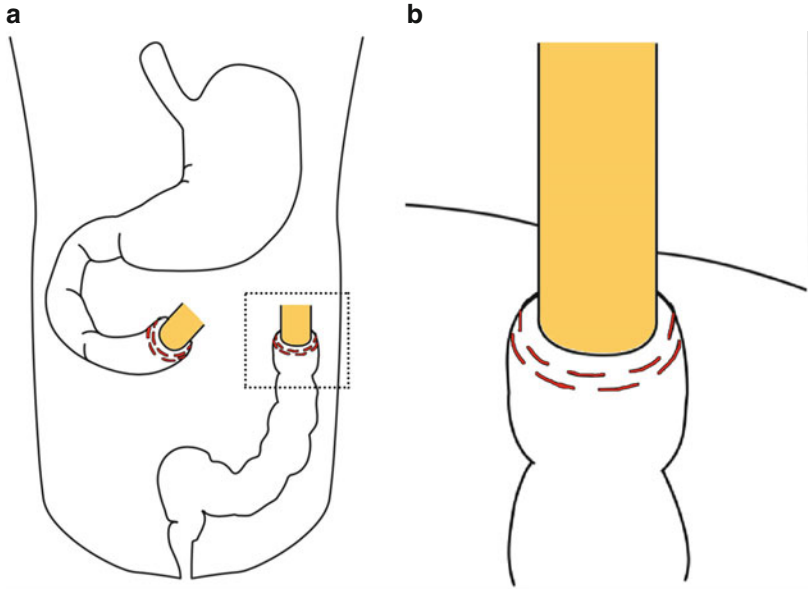

Fig. 10.1 (**a**) Schematic representation of proximal and distal tube stomas. Malecot or Foley catheter is placed into the proximal and distal end of the remnant bowel. (**b**) Enlarged view of the tube stoma. The tube stoma is fashioned using purse string sutures to the abdominal wall. Tube is highlighted in *yellow* and purse string suture in *red*

Every day of CTE, the input and output should be recorded by the family or nurse looking after the patient. Volume of feed, stoma effluent consistency and volume recycled and volume and consistency of stool passed per rectum are important information to understand whether the CTE clamping–recycling is reaching its goal. Furthermore, routine monitoring of blood, urinary sodium and weight and multidisciplinary review are performed weekly.

Complications of Controlled Tissue Expansion

Since 2005 when the CTE clamping–recycling was started in our clinical practice, the most common problems that we have encountered in the programme are vomiting, dislodgement of catheter, sepsis and fluid and electrolyte imbalance.

In case of vomiting, we advise to unclamp proximal tube and to flush catheter to ensure it is not blocked or kinked. In case of a patient with gastrostomy or NG, unclamping these tubes is a good practice to protect the upper airways, to reduce abdominal distension. Vomiting could be also due to the volume of feed. In this scenario, we suggest to reduce the clamping time. Finally, CTE programme may restart after 24 h if the child is well and tolerating feeds.

If dislodgement of catheter happens during the early postoperative period, another catheter is placed under radiological guidance. Occasionally surgery is indicated to replace the catheter. When accidental removal of the tube occurs more than 4 weeks postoperatively, a Foley catheter can be inserted with the balloon inflated just to keep the catheter snug. If there is any doubt, a radiological confirmation is mandatory. Under no circumstances, the catheter should be left in if there is any doubt on its position.

If the child develops sepsis due to a line infection or any other factors, the expansion programme is put to a break until the episode of sepsis is over. The treatment of sepsis in these cases is the same as any other cases with appropriate administration of antibiotics guided by microbiologist's advice and results of cultures.

In case of fluid and electrolyte imbalance, correction of electrolyte disturbances should be performed quickly. Intravenous fluids may

be necessary, and TPN composition should be re-tailored based on the child requirements.

Conclusion

Controlled tissue expansion allows creation of bowel dilatation quicker than physiological intestinal adaptation. Bowel dilatation is an essential asset to perform bowel lengthening procedures. The CTE programme is specifically designed to create tissue to prepare patients for bowel lengthening, and it is not a solution to the short bowel problem in isolation.

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Pediatric Small Bowel Transplantation: An Update

11

Aparna Rege and D. Sudan

Abbreviations

ACR	Acute cellular rejection
AMR	Antibody-mediated rejection
CMV	Cytomegalovirus
CR	Chronic rejection
EBV	Epstein-Barr virus
GVHD	Graft versus host disease
PN	Parenteral nutrition
PTLD	Posttransplant lymphoproliferative disease
rTAG	Rabbit antithymocyte globulin
SBTx	Small bowel transplant

Background

Since its conception in the 1960s, there has been considerable growth in the utilization of intestinal transplantation for the management of patients with intestinal failure. Intestinal failure results from the inability of the gut to absorb fluids or nutrients either due to malfunction or from the lack of adequate absorptive surface secondary to extensive bowel resection. The most common etiology of intestinal failure in the pediatric population includes conditions collectively labeled as short gut syndrome due to necrotizing enterocolitis (NEC), gastroschisis, volvulus, and intestinal atresia. The remaining etiologies of intestinal failure include functional bowel problems with preserved bowel length comprising a large group of conditions such as Hirschsprung's disease, neuronal intestinal dysplasia, neuropathic or myopathic pseudo-obstruction, protein-losing enteropathies, microvillous inclusion disease, and other or unspecified conditions. In a 2010 survey describing the population of pediatric patients on the intestinal transplant wait list, 51 % were less than 1 year old at initial listing and 31 % were 1–5 years of age [1]. The most common conditions at listing were gastroschisis (23 %), other SGS (21 %), necrotizing enterocolitis (19 %), volvulus (12 %), and functional bowel syndrome (12 %) [1]. In the presence of a comprehensive multidisciplinary rehabilitation program, majority of patients with short gut are successfully managed with a combination of enteral and parenteral nutrition (PN) and surgical reconstruction wherever indicated. There are few isolated case series reports of long-term survival on PN alone in patients with irreversible intestinal failure [2, 3]. Most patients with irreversible intestinal failure develop life-threatening complications from long-term PN and eventually progress to intestinal transplantation.

A. Rege, MD (✉) • D. Sudan, MD
Division of Abdominal Transplant, Department of Surgery, Duke University Medical Center, Durham, NC, USA
e-mail: aparna.rege@duke.edu; debra.sudan@duke.edu

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Concept of Intestinal Transplantation

The US Centers for Medicare and Medicaid Services, in October 2000, established intestinal, combined liver/intestinal, and multivisceral transplantation as the standard of care for patients with intestinal failure when total parenteral nutrition (TPN) therapy has failed [4]. According to Medicare, criteria for TPN failure include impending or overt liver failure from TPN-induced cholestasis, loss of venous access due to thrombosis of major central veins, frequent central line-related sepsis, consisting of more than two episodes of systemic sepsis per year, or a single episode of fungemia from central line infection associated with septic shock or acute respiratory distress syndrome or frequent, severe dehydration despite optimal intravenous fluid management.

The relative risk of transplantation vs removal from the transplant wait list due to death or poor general condition varies significantly by the disease causing the intestinal failure. Rates of transplantation are the highest for SGS (75 %) which also seemed to have the least mortality on the wait list, followed by volvulus and gastroschisis which seem to have similar outcomes with >50 % rates of transplantation. NEC on the other hand has significantly poorer outcomes with increased mortality on the wait list (37 %) and decreased rates of transplantation (42 %) [1].

This survival benefit in gastroschisis and volvulus may be partly related to the size and weight of the full- or near-term babies in comparison to low birth weight in NEC babies in addition to the ongoing systemic inflammatory process [5, 6]. Finding appropriate size-match donors for lower-weight infants with contracted abdominal cavities can also impose a challenge, further increasing the time on the wait list. Death on the transplant list is more common in younger (<1 year) and lower-weight patients (<10 kg) signifying the importance of early referral of such pediatric patients to a transplant center for intensive intestinal rehabilitation therapy [1].

Several studies have recommended "early referral" to specialized centers for the optimal and early management of intestinal failure to maximize nutritional status, reduce dependence to TPN, improve intestinal viability, and enable weight gain for successful outcomes after transplantation [7–9]. This is achieved through a multidisciplinary approach including surgery for autologous intestinal reconstruction whenever indicated to lengthen remnant bowel and preclude or delay the need for transplantation. Further reduction in wait-list mortality can be achieved by aggressively improving donor utilization. Centers that have used intestines from relatively stable brain-dead donors receiving cardiopulmonary resuscitation have not noticed significantly different morbidity and mortality outcomes in comparison to cardiologically stable donors [10]. Similarly thoughtful consideration should be given to the use of neonatal and infant donors (<3 months, <5 kg) that are currently underutilized for the risk of increased rate of thrombotic vascular complications [11].

Children with progressive TPN-induced liver disease end up requiring a liver or multivisceral transplant in addition to the intestine, thus contributing to the higher wait-list mortality in this population. With progressive liver failure, death is imminent within 6–12 months of the onset of elevated bilirubin [12]. The main risk factors contributing to death within 6 months of transplant evaluation are elevated plasma bilirubin >100 mmol/L, presence of splenomegaly, and cirrhosis on liver biopsy [13, 14].

Important Surgical Considerations

Procedure Selection

The decision on the type of intestinal allograft depends on patient's existing anatomy and the disease process. Various selection options include:

1. *Isolated small bowel transplantation* (Fig. 11.1) when liver function is preserved in cases of intestinal failure. The superior mesenteric artery of the donor bowel is anastomosed to the infrarenal aorta, and the donor

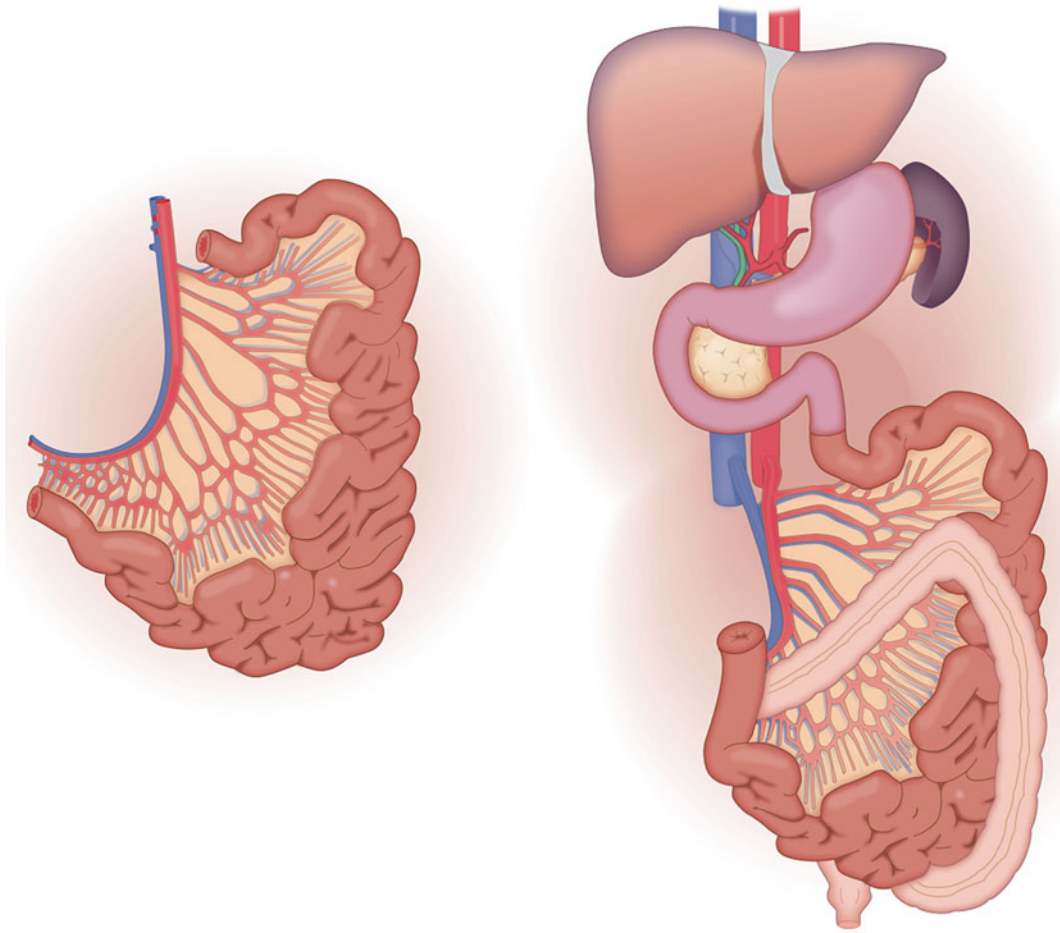

Fig. 11.1 Isolated intestinal transplant: transplantation of isolated small bowel with anastomosis of superior mesenteric artery and vein to the infrarenal aorta and inferior vena cava, respectively

superior mesenteric vein is anastomosed to the recipient superior mesenteric vein, portal vein, or inferior vena cava.

2. *Small bowel and liver transplantation* when intestinal failure is associated with PN-induced liver failure. In this case when the native stomach, duodenum, and pancreas are preserved, a native portacaval shunt is performed for venous drainage of the preserved native viscera. The liver and bowel with the allograft duodenum are typically procured en bloc to maintain the integrity of the allograft biliary system (Fig. 11.2a). During implantation, the hepatic veins of the donor liver are anastomosed to the native cava either by the piggyback or the caval replacement technique, and the donor aorta with the double arterial stem of the celiac and superior mesenteric arteries is connected to the infrarenal aorta (Fig. 11.2b) or to the supraceliac aorta (Fig. 11.2c) using a donor aortic conduit. Alternatively, the native stomach, duodenum, and pancreas may be removed and the proximal GI tract reconnected by gastrojejunostomy between the native stomach remnant and the proximal donor jejunum (and no need for portacaval shunt placement). In addition to the en bloc technique typically performed, the liver and bowel graft can be procured separately and implanted separately without the duodenum and pancreas. However this technique is associated with higher rates of complications

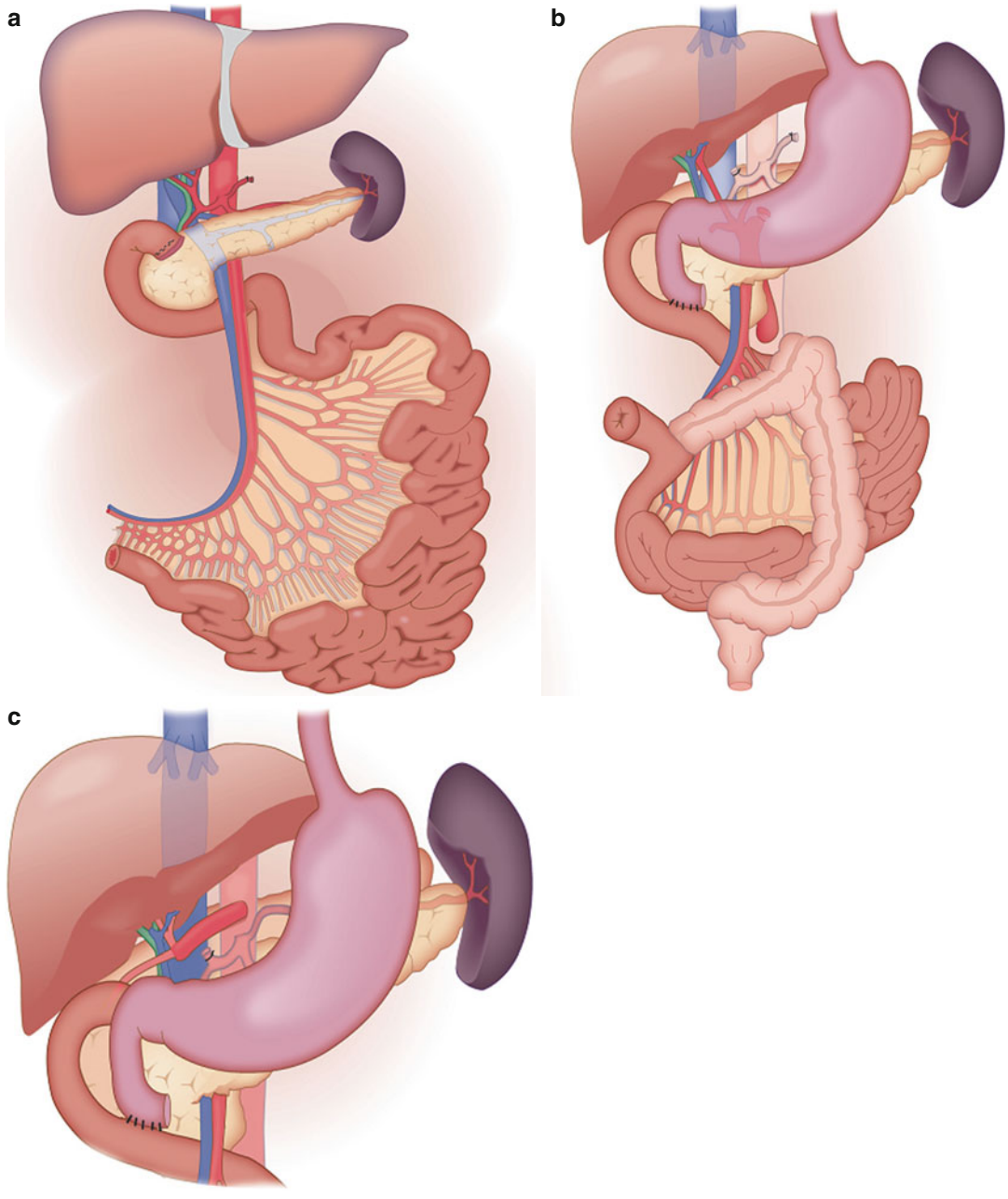

Fig. 11.2 (**a**) Allograft for combined small bowel and liver transplant. The liver and bowel with the allograft duodenum and donor pancreas are procured en bloc to maintain integrity of the allograft biliary system. (**b**) Infrarenal placement of the donor aortic conduit in a combined small bowel-liver transplant. (**c**) Supraceliac placement of the donor thoracic-aortic conduit for combined small bowel-liver transplant

and is therefore not the preferred method at most centers.

3. *Multivisceral transplantation* when the recipient suffers from severe gastric dysmotility, some centers elect to remove the native stomach, duodenum, and pancreas in addition to removal of the native liver and small bowel. Other situations in which explant of the native

foregut may be beneficial include extensive venous thrombosis of the portal and superior mesenteric system precluding a portacaval shunt or severe dysfunction of the pancreaticoduodenal complex due to trauma, chronic pancreatitis, slow-growing tumors like desmoids, and intestinal pseudo-obstruction with associated severe gastroparesis. Implantation of the multivisceral graft involves the suprahepatic venous anastomosis as above for liver/intestine grafts followed by the aorto-aortic conduit anastomosis without the need for a native portacaval shunt.

4. *Liver-alone transplantation* in patients with intestinal failure who are progressing toward enteral independence with intestinal adaptation but in the process have developed PN-induced liver failure. In such patients when at least 50 % enteral tolerance is achieved in the absence of underlying intestinal absorptive disorder, intestinal transplantation may be avoided. This usually occurs in kids less than 2 years of age, and complete enteral tolerance is achieved with ongoing adaptation after replacement of the diseased liver [15].
5. *Living donor intestine grafts* used either as an isolated intestine graft or as a combined bowel graft with left lateral liver segment (from the same donor) can also be another viable option. Although not routinely practiced, there have been isolated case reports of this particular technique [16].

The Appropriate Donor

A proper size match between the donor and the recipient is of particular importance in pediatric transplantation as loss of domain from prior extensive bowel resections is not uncommon. Occasionally reduction of the liver graft (leaving behind the left or right lobe only) and variable reduction of the intestine allograft may be essential to facilitate abdominal closure with the use of a larger donor [17]. Alternatively, an increase size of the abdominal cavity can be achieved with alternate abdominal closure techniques as noted below.

Abdominal Wall Closure

Abdominal wall closure can often be a challenge in short gut pediatric patients due to loss of domain requiring innovative wound closure techniques such as the use of the fascia of the rectus muscle (FoRM) from the same donor as a vascularized [18] or nonvascularized tissue allograft [19]. Sometimes enlargement of the abdominal domain with the use of temporary coverage with prosthetic materials enables a staged closure. Alternatively abdominal closure can be achieved by skin closure alone, by using acellular dermal matrix or other biologic tissue replacement products, rotational flaps, advancement of rectus muscle fascia, or abdominal wall grafts [20].

Utility of the Colon

Early experience incorporating the colon as part of the intestinal allograft was faced with graft loss from infectious complications, thereby increasing the morbidity and mortality. More recent studies however suggest that colonic inclusion has a favorable impact on the clinical outcomes in intestinal transplantation. The presence of the colon with an intact ileocecal valve has been shown in patients with secretory disorders by enhancing fluid absorption and minimizing dependency on intravenous fluid supplementation post ileostomy closure [21, 22].

Immunosuppression: What's New?

Initial attempts at intestinal transplantation were largely unsuccessful due to the lack of reliable immunosuppression to control the aberrant immune response in a highly immunogenic, lymphocyte-rich intestinal allograft [23]. Immunosuppression management in intestinal transplantation has evolved over the past several years. The most important impact was made with the introduction of tacrolimus in the 1990s, transforming an experimental procedure into a reality for patients with irreversible intestinal failure [24, 25]. Other immunosuppression regimens

that have been evaluated include a combination of tacrolimus and steroid maintenance alone, to the addition of induction therapy with cyclophosphamide or daclizumab and in recent years with rabbit antithymocyte globulin (rATG). Additional immune modulation of the allograft with either in vivo antilymphocyte therapy to the donor with an attempt to reduce the incidence of post-transplant acute cellular rejection associated with graft loss or ex vivo intestinal allograft irradiation to eliminate the risk of graft versus host disease (GVHD) also became a routine practice [26, 27]. Donor bone marrow augmentation was also used in select centers in attempts at developing chimerism and enhanced graft acceptance with the infusion of 3–5 × 10^8 donor bone marrow cells/kg recipient body weight. However, this attempt has not improved overall rejection rates or graft survival [28]. Aggressive immunosuppression strategies are fraught with significant infectious complications and drug toxicities and an unresolved challenge of graft loss from chronic rejection.

Complications

Rejection

Rejection continues to be the major cause of allograft failure after intestinal transplantation, affecting approximately 50–60 % of pediatric recipients, with severe rejection in as many as one third of recipients in the first 90 days after transplantation [29]. The intestinal allograft is highly immunogenic, loaded with donor lymphoid tissue, and it is hypothesized that this can stimulate host immune reactivity leading to a higher propensity for rejection than other solid organ allograft recipients. While the mechanism for the increased immunogenicity of the bowel graft is not well understood, several observations have been made including an association between elevated myeloid/plasmacytoid dendritic cell ratio and early acute cellular rejection (ACR) in pediatric small bowel transplantation [30, 31]. Various other cellular mechanics of rejection include macrophages in both the allograft and host, donor T-cytotoxic (Tc) cells, and donor-specific inflammatory CD154 T cells [32–34]. Macrophages can be controlled by donor pretreatment with polyclonal lymphocyte depletion. Patients prone for ACR are commonly found to have donor-specific inflammatory CD154 T cells. The presence of donor T-cytotoxic (Tc) cells indicates a possibility of developing drug resistance leading to recurrent rejection episodes. More recently NOD2 gene has been implicated in severe ACR and graft loss in a small population of pediatric and adult SBTx recipients [35]. NOD2 gene in response to gut pathogens induces an unregulated aberrant innate immune signaling involving helper T cell, creating a cytokine-rich inflammatory response.

Treatment of ACR is not standardized; however, it is primarily aimed at the cellular component, and at some centers the treatment is based on the severity of the rejection process. Most cases of mild rejection respond well to 3–5 days of intravenous methylprednisolone 20 mg/kg, with optimization of serum tacrolimus levels to 15 ng/mL. Severe exfoliative rejection or steroid-resistant rejection requires treatment with antilymphocyte antibodies like rATG, up to 10 mg/kg, in 5–7 divided doses. Testing serum CD3 levels can help confirm lymphocyte depletion and provide guidance on the duration of treatment required. A posttreatment biopsy to gauge the response to treatment is routine. The risk of acute rejection has diminished to 30 % with alemtuzumab induction and 62 % with rATG induction in comparison to a rate of 80 % with the pre-rATG immunosuppressive protocols. Severe rejection however has been associated with a high mortality rate (up to 50 %) due to the risk for bacterial translocation and systemic infection during the period of mucosal denudation.

The role of humoral immunity in mediating rejection in intestinal transplant recipients has been increasingly recognized. A routine use of cross-match (virtual or prospective) has helped minimize the incidence of antibody-mediated rejection (AMR) from pre-existing donor-specific antibodies (DSAs) [36]. There is considerable controversy however in this regard; while some clinicians have implemented strategies to desensitize recipients with preformed antibodies with the use of plasmapheresis and immunoglobulin therapy at the time

of transplant [37], others have demonstrated that preformed antibodies are related to AMR [38]. Furthermore, histological findings of AMR are not universally accepted or defined.

Chronic rejection (CR) is observed in 10–15 % of patients and is considered as an important cause of graft loss after the second year of intestinal transplantation [39]. CR is fivefold more common with isolated small bowel transplant in the absence of a liver allograft. De novo DSAs, appearing in one fourth of patients after bowel transplants, have been shown to be closely associated with chronic rejection and graft loss [40, 41]. The clinical presentation includes diarrhea, weight loss due to protein-losing enteropathy, and chronic abdominal pain. The onset is insidious and often difficult to diagnose. A definitive management of CR requires re-transplantation.

Reasonable long-term outcomes have now been achieved (71 % survival at 4 years) following re-transplantation for CR [41]. Handling preformed antibodies at the time of re-transplantation can pose a major challenge.

Allograft Rejection Histopathology

Close monitoring of the intestinal allograft by frequent endoscopy and histopathologic examination of allograft biopsies is still the gold standard for identifying early rejections and assessing the integrity of the graft. Pathologists are exploring ancillary tools like molecular biomarkers to further identify and characterize the rejection process. Histologically, rejection is graded by the degree of epithelial damage based on three parameters: (1) the extent of mucosal injury, (2) the degree of inflammatory infiltration, and (3) the crypt apoptotic body count or degree of destruction. Mild rejection is characterized by increased crypt apoptosis with intact surface epithelium. In moderate rejection, crypt damage is more severe with architectural distortion and villous blunting with edema and congestion. Severe rejection may lead to marked architectural distortion with crypt damage, crypt loss, and erosion of the surface epithelium. Regeneration occurs by reepithelialization over the surface of a lamina propria devoid of crypts. Chronic rejection which is the main cause of late intestinal graft dysfunction and loss is characterized mainly by allograft obliterative vasculopathy with marked intimal hyperplasia in submucosal or mesenteric arteries, identified only on full-thickness intestinal biopsies. Mucosal biopsies are noncontributory to the diagnosis of CR but may show mild ischemic changes, low-grade apoptosis, and possibly mild fibrosis of the lamina propria [42, 43].

Graft Versus Host Disease

Graft versus host disease (GVHD) results from reaction of donor-derived lymphocytes and inflammatory cytokines against host tissues through microchimerism. Donor-immunocompetent cells damage the host skin, native liver, native intestine, and bone marrow resulting in symptoms like generalized maculopapular rash, diarrhea, pulmonary symptoms, and hematologic abnormalities including pancytopenia, myeloid dysplasia, and autoimmune hemolytic anemia [44]. GVHD is more common after multivisceral transplant in comparison to isolated intestinal transplantation, with an incidence of less than 10 % and mostly cutaneous involvement. Extensive GVHD with BM involvement is usually associated with high morbidity and mortality [45]. Treatment usually involves reduced immunosuppression and high-dose steroids. Occasional steroid nonresponders are managed with other agents like sirolimus, mycophenolate mofetil, pentostatin, etc. Various other agents like monoclonal antibodies such as infliximab (anti-CD20) and anticytokine therapies like etanercept (antitumor necrosis factor-a [TNF-a]) and daclizumab (anti-interleukin [IL]-2 receptor) have been used successfully to treat steroid-resistant GVHD following allogeneic stem cell transplantation [46–48].

Infections

Infectious complications add significant mortality and morbidity in patients with intestinal transplantation. Pediatric patients carry a 90 % risk of

acquiring bacterial infections within 6 months after intestinal transplantation, with the risk of bacteremia being higher than in adults [49]. The immense microbial burden of the intestinal allograft, the complexity of the procedure, the high levels of immunosuppression required, and the higher incidence of acute rejection with bacterial translocation through a damaged mucosa are all contributory to the high incidence of bacteremia in this population. Severe hypogammaglobulinemia after intestinal transplantation may be another important factor that can have an adverse impact on infection-related morbidity and mortality [50]. Although not proven, frequent monitoring of IgG levels and replacement with intravenous immunoglobulins in recipients with low levels in the early posttransplant period have been suggested to minimize the incidence and severity of posttransplant infections [50].

The predominant causative organisms isolated in the order of frequency include gram-positive cocci, mainly the *Enterococcus* species, gram-negative bacteria, and *Candida* species [51]. Intra-abdominal infection within the first 6 weeks of transplant is associated with a high mortality rate. The incidence of multidrug-resistant infections is also high (50%); hence, the antimicrobial resistance pattern needs to be considered when planning empiric coverage in the peri-transplant period [52].

Viral enteritis is another significant infection, usually occurring after 6 weeks posttransplantation. Various viruses known to cause disease include adenovirus, norovirus, rotavirus, and double-stranded DNA viruses of the herpesvirus family, i.e., cytomegalovirus (CMV) and Epstein-Barr virus (EBV). Clinically, viral enteritis is often indistinguishable from allograft rejection with similar symptomatology, and hence separating the two is very important since management of viral infection includes reduction in immunosuppression. Besides bowel biopsy, serum and tissue DNA polymerase chain reaction (PCR) and immunohistochemistry can help in securing the correct diagnosis. Viral enteritis can cause protracted diarrhea and severe dehydration in pediatric patient often requiring intravenous fluid resuscitation and even temporary PN. Viral infection is associated with immune activation, and this in combination with the potential for reduced absorption of immunosuppressive medications in the presence of diarrhea increases the incidence of acute rejection to 69% [53]. Occasionally, multisystem involvement from disseminated adenovirus infection, in the presence of significant immunosuppression, can lead to 20% mortality necessitating the use of antiviral agents like cidofovir [54].

Cytomegalovirus (*CMV*) *infections* are a major source of morbidity after intestinal transplantation with an incidence of 18% in the pediatric recipient and a 7% risk of invasive disease [55]. Symptoms can vary from fever, myalgia, and leukopenia in CMV viremia to elevated liver enzymes, increased ileostomy output, or gastrointestinal bleeding with tissue-invasive disease. Matching the CMV serology of the donor and the recipient should ideally be sought but is not always feasible. A CMV mismatch recipient (donor+/recipient – status) is at the highest risk of developing invasive CMV, recurrent CMV, and ganciclovir-resistant CMV. Hence, intensive serum CMV PCR monitoring after transplantation should be employed for early detection of CMV viremia; however, the possibility of having undetectable serum CMV PCR in the presence of tissue-invasive disease has been described [55]. Prophylaxis protocols although center specific usually include ganciclovir or oral valganciclovir for a duration of 3–6 months; occasionally CMV hyperimmune globulin has also been described in recipients of CMV-mismatched allografts. Treatment on the other hand involves not only ganciclovir or oral valganciclovir but also requires reduced immunosuppression.

Infection with *Epstein-Barr virus (EBV)*, a herpesvirus family, is another significant viral infection more commonly found in intestinal transplant patients than any other type of solid organ transplantation. EBV viremia has been associated with posttransplant lymphoproliferative diseases (PTLDs) including early, polymorphic, monomorphic, and classic Hodgkin lymphoma-type lesions. The incidence of PTLD is in the range of 5–10% for pediatric organ recipients and is higher, 12–20%, in patients with intestinal and multivisceral grafts compared to other

solid organ graft recipients [56]. Risk factors for PTLD include a pediatric patient younger than 5 years of age, high levels of immunosuppression such as the use of anti-T-cell antibodies, recipient EBV seronegativity at the time of transplant, and high circulating levels of EBV posttransplant [57, 58]. Most PTLDs in the pediatric age group are EBV positive, after the development of primary EBV infection in the early posttransplant period. However, the incidence of EBV-negative PTLD giving rise to monomorphic plasma cell lesions like atypical plasma cell hyperplasia or plasmacytoma-like lesions appears to be increasing in the adult population [59]. Serial monitoring of EBV viral load in peripheral blood with EBV DNA PCR monitoring and high index of suspicion is needed to detect PTLD. Imaging with computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET) scan and bone marrow biopsy provide staging of PTLD, whereas biopsy of the accessible nodal tissue provides histopathologic confirmation of the diagnosis [60, 61].

The therapy for PTLD focuses around reduction of immunosuppression and resection of localized lesions if necessary. Refractory PTLD is treated successfully with chemotherapy regimen of cyclophosphamide and prednisone with addition of rituximab, an anti-CD 20 antibody [62]. Prognosis depends on disease dissemination and response to reduction of immunotherapy.

Renal Insufficiency and Chronic Kidney Disease

Renal failure is another significant morbid complication of intestinal transplantation that warrants transplantation of another organ. A prolonged use of high-dose tacrolimus in an attempt to ward off rejection is the major responsible factor for renal insufficiency, with cumulative concentration of tacrolimus predicting the reduction in the glomerular filtration rate [63]. Other contributory factors include the use of nephrotoxic antimicrobials due to the increased incidence of infections, frequent hypoperfusion, and dehydration from pretransplant short bowel syndrome or posttransplant elevated stool or ostomy outputs and chronic hypertension from the use of immunosuppressive agents. The incidence of chronic kidney disease in adult intestinal and multivisceral transplant recipients 5 years after transplantation has been reported as high as 21.3 %, higher than in other solid organ transplant populations [64].

Outcomes

Patient and graft survival after intestinal or multivisceral transplantation have steadily improved over the past decade. According to the 2013 OPTN report on intestinal transplantation, the number of recipients alive with a functioning intestine graft has steadily increased since 2002, to 1012 in 2013; almost half of them being pediatric intestine-liver transplant recipients (Fig. 11.3). For intestine transplants in 2008, 1- and 5-year graft survival was 73.1 and 62.3 %, respectively, for recipients less than 18 years old and 78.6 and 48.0 %, respectively, overall for recipients of intestine transplant alone compared to 70.6 and 48.9 %, respectively, for combined intestine-liver recipients [65].

Patient survival was superior for intestine-alone recipients compared with intestine-liver recipients, regardless of age. Patient survival is lowest in adult intestine-liver recipients (1- and 5-year survival, 69.1 and 46.1 %, respectively) and highest in pediatric intestine-alone recipients (1- and 5-year survival, 89.2 and 81.4 %, respectively) [65] (Fig. 11.4).

Transplant	Survival	1 year (2008–2009)	5 years (2008–2013)
SBTx <18 years	Graft survival	73.1	62.3
SBTx >18 years	Graft survival	76.1	37.5
Intestine	Graft survival	78.6	48
	Patient survival (pediatrics)	89.2	81.4
Liver-intestine	Graft survival	70.6	48.9
	Patient survival (adults)	69.1	46.1

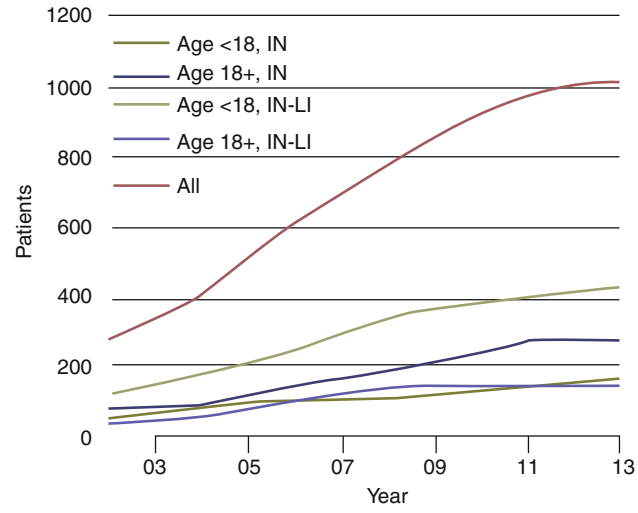

Fig. 11.3 Recipients alive with a functioning intestine graft on June 30 of the year, by age at transplant

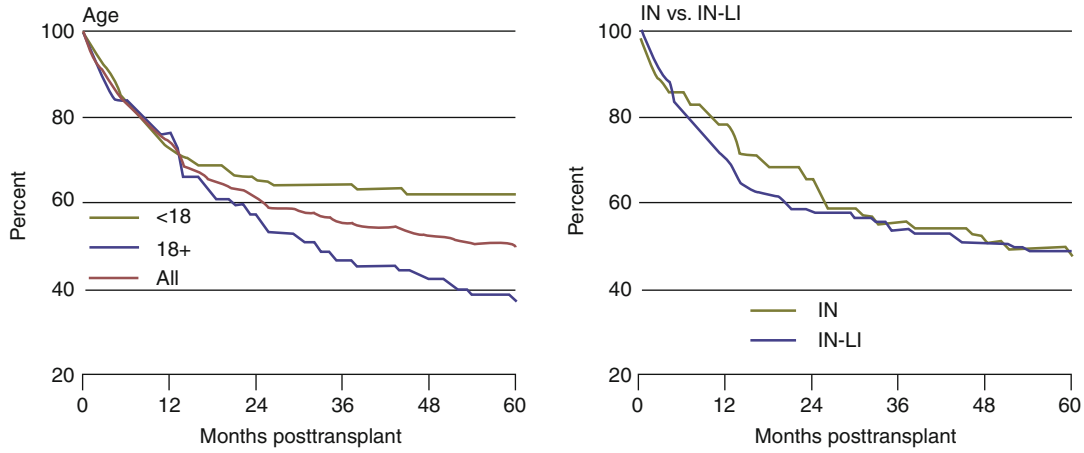

Fig. 11.4 Graft survival among intestine transplant recipients, 2008, with respect to age and type of transplant

According to the 2013 ITR report, of the patients surviving more than 6 months after transplantation, 67 % are free from TPN and 25 % require either partial supplementation or full TPN or IV hydration. In patients receiving a colon segment with their intestine graft, there is a 5 % higher rate of freedom from parenteral nutrition or IV fluid support [66]. However, as a result of existent denervation and a lack of lymphatic drainage of the transplanted bowel, micronutrient deficiency and fat malabsorption often require an ongoing supplementation and ongoing need for antimotility agents [67]. Positive weight gain and growth reported in pediatric recipients indicate successful gastrointestinal autonomy can be achieved after intestinal transplantation as suggested from the freedom from parenteral nutrition and intravenous hydration and positive growth and weight gain reported [68].

Quality of Life After Intestinal Transplantation

A high incidence of neuropsychiatric disorders (24 %) has been reported in pediatric intestine transplant recipients including developmental delays and neurological and behavioral disorders. Combined effect of the underlying gastrointestinal disorders, long-term parenteral nutrition, and complication posttransplantation has been implicated as a cause of these disorders. Various factors suggested to contribute include brain atrophy, cerebral vascular insufficiency from multiple septic emboli, micronutrient deficiencies, trace element toxicities, and liver failure-induced metabolic encephalopathy [69, 70].

Despite these reports, high Lansky and Karnofsky performance scale scores in this population imply a good to excellent quality of life, with preserved cognitive, psychosocial, and physical functions similar to healthy normal children. These results could be biased due to the fact that assessment of quality of life (QOL) after intestinal or multivisceral transplantation in infants and younger children may be difficult due to the lack of appropriate tools. Existing studies report that beyond the perioperative period, children perceive their physical and psychosocial functioning as similar to normal schoolchildren [71, 72]. However parental perception differs with overall sense of decreased general health and physical functioning for their child following intestinal transplantation.

Conclusion

Improved outcomes following intestinal transplantation have expanded its application for patients with irreversible intestinal failure. However, management following transplantation remains extremely challenging with a high incidence of complications including infections and acute rejection. Other challenges that need to be addressed include transplantation of highly sensitized patients, management of de novo donor-specific antibodies, and avoidance of graft failure from chronic rejection. Future research needs to be directed toward immunological strategies that promote tolerance and allow less potent immunosuppression. Additional areas of improvement include identification of the appropriate candidate for referral and the ideal timing for transplantation.

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Intestinal Regeneration

12

Tracy Grikscheit and Paolo De Coppi

Abbreviations

BMP	Bone morphogenetic protein
CBCCs	Crypt base columnar cells
ENS	Enteric nervous system
ESCs	Embryonic stem cells
FGF	Fibroblast growth factor
GLP-2	Glucagon-like peptide-2
Ihh	Indian hedgehog
iPSCs	Induced pluripotent stem cells
ISCs	Intestinal stem cells
OUs	Organoid units
PDGF	Platelet-derived growth factor
PGA	Polyglycolic acid
PLLA	Poly-l-lactic acid
SBS	Short bowel syndrome
Shh	Sonic hedgehog
TA	Transit amplifying
TESI	Tissue-engineered small intestine
TPN	Total parenteral nutrition
VEGF	Vascular endothelial growth factor

T. Grikscheit, MD, PhD
Developmental Biology and Regenerative Medicine Program, Saban Research Institute, Children's Hospital Los Angeles, Los Angeles, CA, USA

P. De Coppi, MD, PhD (✉)
Stem Cells and Regenerative Medicine, DBC, Institute of Child Health, University College London, and Great Ormond St. Hospital for Children, 30 Guilford Street, London WC1N 1EH, UK
e-mail: p.decoppi@ucl.ac.uk

Introduction

The small intestine is a vital organ that achieves homeostasis through tissue growth and maintenance. Its loss may lead to variable degrees of absorption debilities, such as short bowel syndrome (SBS). In previous chapters, we have looked at alternative therapeutic options to treat SBS; however, this is an area of unmet clinical need. While strategies such as the increase of intestinal surface area could help by partly restoring the absorption level to that of the healthy organ, at the moment only total parenteral nutrition (TPN) and bowel transplantation are real long-term options for these patients. However, as discussed in this volume, TPN is associated with line infections, deep venous thrombosis, and liver failure, while intestinal transplantation is limited by organ shortage and the need for immunosuppression. Therefore, there is a need for innovative solutions which would allow a better quality of life and a higher survival rate for patients with SBS [1].

The intestine, similar to other epithelial organs, undergoes constant epithelial renewal, thanks to the presence of highly proliferative resident stem cells. Intestinal stem cells (ISCs) are present in the crypt and maintain the pool of precursor and differentiated cells, which are shed from the tip of the villi after a journey of 7–10 days from their production at the base of the crypt [2]. This highly specified environment,

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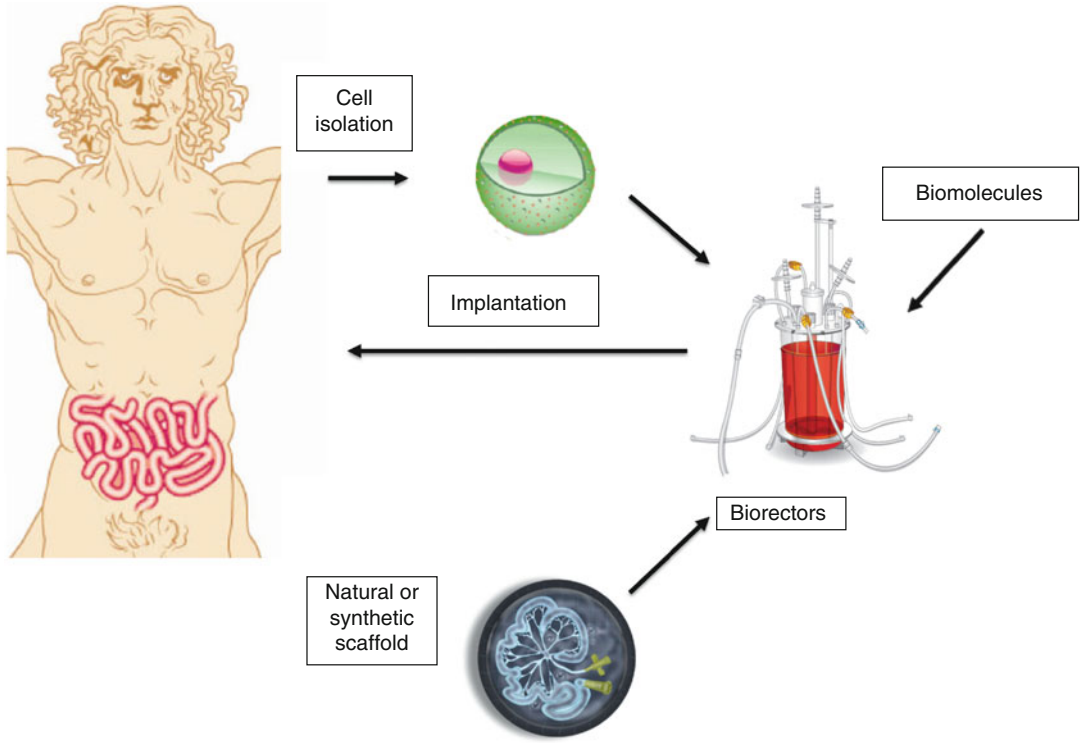

Fig. 12.1 Tissue engineering. A tissue-engineered intestinal construct may be created by the combination of a scaffold and cells, grown in a bioreactor and transplanted in patients. A three-dimensional scaffold may be created from synthetic material, collagen, or a decellularized matrix. Cells for the use of tissue engineering are derived from a number of sources such as the adult, the fetus, and the embryo. Additionally, biomolecules may be co-transplanted with the aim of ameliorating cell integration, survival, and differentiation

together with the supporting mesenchyme, appears to be crucial for the preservation of the intestine physiology, and its understanding has helped in developing possible therapeutic approaches [3]. While a limited number of hollow organs such as the trachea, urethra, and vagina have been initially transplanted to patients, more complex tubular structures such as the intestine require further experimental work prior to translation. Although pioneering investigations in the field of intestinal bioengineering date back to the 1980s [4], initial excitement has been blunted by the considerable limitations and roadblocks encountered in the course of experimental investigations. While simpler tissue-engineered organs such as the trachea and bladder have been adopted clinically, a major hurdle for the intestine is the complexity of its anatomy and functions [5, 6] (Fig. 12.1).

We will review here the advancements of tissue-engineered small intestine (TESI) research and the potentially vital combination of stem cells and biopharmaceuticals to improve the quality of life and life span of patients suffering from SBS.

Adult Stem Cells

TESI originated in the late 1980s in Vacanti's group. By seeding mouse and rat cells and cell clusters from different origins onto biodegradable, polymeric scaffolds and implanting them into host animals, they obtained satisfactory cell viability, proliferation, and engraftment rates [7]. The development of isolated organoid units (OUs) from the intestine of the suckling rat to produce all of the epithelial cell lineages represented an

important step forward. In an adaptation from a method elaborated by Evans et al. in the early 1990s, the Vacanti group reported the generation of TESI in vivo. Cells were isolated in the form of organoid units (OU), which consisted of multicellular clusters of epithelium and mesenchyme [8]. Organoid units isolated through enzymatic digestion were seeded on tubular polyglycolic acid (PGA) scaffolds sprayed with 5 % poly-l-lactic acid (PLLA) and transplanted heterotopically. Consistent results showed that OU survived and formed a complex composite that resembled a small intestine, indicating that morphogenesis, cytodifferentiation, and phenotypic maturation of the organ had occurred [9, 10]. Interestingly, TESI rescued rats subjected to 75 % small bowel resection after anastomosis to the native intestine in an end-to-end fashion [11, 12]. Later studies would show that tissue-engineered intestinal tissues were capable of generating a mature immune system with macrophages, T, B, and NK cells, and of presenting SGLT1 transporter expression [13, 14]. Similar results were later obtained using xenograft models with transplantation of TESI based firstly on human fetal intestinal cells [15, 16] and more recently postnatal large and small intestinal tissue. The human TESI developed similarly to reported murine TESI, forming crypts and villi with all four specialized epithelial cell types, mucosa, and a mesenchyme from human origin with cells expressing muscular and neural markers [17].

While innovative and efficient in the functional regeneration of the intestine, OUs are difficult to expand in culture, and therefore replacement of large amounts of autologous intestine still requires further development [18]. Recent work done both on the optimization of intestinal epithelial stem cells and on the derivation of intestinal cells from pluripotent stem cell could however overcome these limitations.

The former has been advanced thanks in particular to the work done by Clevers's group, which has shown in the last few years how ISC which reside in the base of Lieberkuhn crypts and express Lgr5 [8, 19] can be isolated and expanded in culture in defined conditions and still capable of building crypt-villus structures in vitro without any mesenchymal niche [20]. As these cells can be reliably expanded in culture, they could represent the ideal source of progenitor cells for intestinal bioengineering. Work by Cheng and Leblond [21] provided evidence that intestinal stem cells located in the crypts, also known as crypt base columnar cells (CBCCs), were pluripotent, responsible for generating the four differentiated cell types of the intestinal epithelium. Many ISC markers have been proposed, namely, Bmi1, Lgr5, CD133, DcamKL-1, and Musashi [20, 22–24]. In the intestine, leucine-rich repeat-containing G-protein-coupled receptor (Lgr5) is exclusively expressed in CBCCs, which are truly capable of forming "crypt-like structures" and all of the four differentiated cell types of the intestine in vitro. In addition, Lgr5- and CD133-positive cells are located at sites at the base of the crypt [25–27] and are capable of dividing to generate the large amount of specialized cells the intestine requires for performing its function properly [28]. The niche stem cells guarantee a constant production of progenitor cells that proliferate following the dogmatic crypt-villus axis and proliferate four to five times becoming transit-amplifying (TA) cells, before differentiating, and subsequently shed at the tip of the villi [29, 30].

Pluripotent Stem Cells

Alternatively, intestinal cells could be derived from pluripotent stem cell. However, one of the major obstacles for engineering organs is the purity and lack of oncogenic potential of the required large-scale donor cell population [31]. When millions of cells are required for a therapeutic effect, it is difficult to make sure none of these still maintain characteristics of pluripotency. When smaller numbers of cells are required, it is easier to make sure they all have reached terminal differentiation as it has been recently reported for macular degeneration of the retina. Retina transplantation has been successfully achieved because of the lower number of cells required and also the immunoprivileged site where allergenic cells can engraft without being

triggered by the immunological system [32]. Functional differentiation of ES and iPS cells toward intestinal epithelium and, more recently, neural crest cells has been successfully achieved and could offer a clinical opportunity also for individuals who have lost their entire intestine with no other options for an autologous treatment. Enteric nervous system (ENS) precursors derived in vitro are capable of targeted migration and colonization of the adult mouse colon with the potential for rescuing a Hirschsprung mouse model [33]. Human pluripotent stem cells [both embryonic (ESCs) and induced pluripotent stem cells (iPSCs)] have been directly differentiated in vitro to form a tissue resembling that of the fetal intestine, presenting secretory and absorptive functions [34]. Human intestinal organoids demonstrated digestive functions and were responsive to systemic signal from the host. [35]. Even though mesenchymal markers forkhead box F1 (FOXF1) and vimentin detected through immunofluorescence and anatomical microscopic analysis indicated the presence of a mesenchymal layer in the formed tissue, it lacked blood vessels and nerves. Fetal enterospheres can also be established during differentiation of human iPS cells. Following transplantation in a colonic injury model, fetal enterospheres contributed to regeneration of colonic epithelium expressing region-specific differentiation markers [36].

Biomolecules

Because of the highly specialized signaling required to both maintain the stem cell niche and promote functional differentiation, engineering of a functional intestine requires not only the combination of functional cells with the capacity of regeneration with a scaffold that would promote functional integration but also the interaction of specific ligands capable to promote the reconstitution of an environment that can respond to the physiological stimuli. Although representing only an initial step toward the ultimate goal of generating a fully functional intestine, decellularized matrices may help to recapitulate a functional structure and may represent in the midterm a bridge for transplantation since any complex structure may be difficult to mimic artificially [37]. However, understanding the different molecules involved at different level will be essential to the engineering of a functional intestine.

While the vascular architecture around the engineered intestine is found to be similar to that found in the native intestine [7], the concentration of antigenic growth factors such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) in the engineered intestine is significantly lower than that found in the juvenile bowel [38]. Similarly, specific signals are important for both niche maintenance and the generation and maintenance of a normal crypt-villi unit. Stem cells and TA cells are regulated by the evolutionarily conserved canonical Wnt/β-catenin signaling pathway, which targets Lgr5 expression and is thought to be the master activator of intestinal crypt proliferation [29, 39–41]. Wnt blocks β-catenin degradation, resulting in stabilization and translocation to the nucleus where it forms β-catenin/TCF complexes [2]. The absence of Wnt signal targets β-catenin for degradation through the ubiquitination/proteasome pathway, elicited by the destruction complex composed of APC, Axin, CKI, and GSK3.74, 75, and 76. β-Catenin-mediated gene expression determines the physical structure of the ISC niche, in coordination with Ephrins and Eph proteins, which control cell migration patterns. The nuclear/cytoplasmic β-catenin pattern indicates that Wnt acts forming a gradient along the crypt axis, with its signaling components being shown to be present in both epithelial cells of the crypt and mesenchymal cells [42]. Interactions between the intestinal epithelium and the mesenchyme also occur through the hedgehog, platelet-derived growth factor (PDGF), and bone morphogenetic protein (BMP) pathways. The sonic hedgehog (Shh) and Indian hedgehog (Ihh) ligands are expressed in the small intestine epithelium of the mouse, becoming concentrated to intervillous regions as villus formation occurs. Conversely, receptors (Ptch1 and Ptch2) and effectors (Gli1, Gli2, and Gli3) are constrained to the mesenchyme lying beneath [43]. Hedgehog is proposed

to be essential for villus establishment but negatively regulates crypt formation. PDGFA is also produced in the epithelium, with its receptors located in the mesenchyme. This signaling pathway is important for villus shaping and control of mesenchyme behavior [44]. For BMP signaling, on the other hand, opposite expression patters are found: BMP2 and BMP4 ligands are produced in the mesenchyme and their receptor (BMPR1A) is present in the endothelium. Indeed, BMP pathway activation is higher in the villus epithelium, and BMP acts as a hedgehog mediator and a blocker of ectopic crypt formation [30, 45, 46].

Similarly, adding regulatory molecules to the developing engineered intestine may be a required and useful approach. Glucagon-like peptide-2 (GLP-2), produced by enteroendocrine cells, induces intestinal hyperplasia in patients and has been reported to control expression and activity of an intestinal transporter [47]. When GLP-2 was administrated to rats bearing TESI anastomosed to the jejunum, there was improved intestinal function of the TESI, with higher villi, deeper crypts, higher crypt cell proliferation, and reduced apoptosis of epithelial cells, when compared to controls [48]. Moreover, loading GLP-2 onto PGA disks before seeding rat OUs augmented the number of tissue-engineered intestinal complexes.

Insufficient vascularization is a common hurdle for engineered organs, precluding proper influx of nutrients and oxygen and, consequently, proper growth and function. Initial efforts to prevascularize biodegradable polymers to ameliorate cell attachment and growth had not employed additional biologicals in the composite [49, 50]. Angiogenesis is the growth of blood vessels from the pre-existing vasculature. Vascular endothelial growth factor, for instance, comprises a group of proteins belonging to the PDGF/VEGF growth factor family. As key mediators of physiological and pathological angiogenesis and lymphangiogenesis, these proteins are therapeutic targets in several disease contexts [51]. In an effort to improve the vascular architecture of TESI, a pro-angiogenic VEGF isoform was encapsulated in poly(lactide-co-glycolide) (PLGA) microspheres and loaded into molded scaffolds containing intestinal OUs. The microspheres provided a sustained delivery of VEGF culminating in an increased vascular net outside the developing organs (CD31 staining), which also grew larger and denser than the control counterparts. Moreover, epithelial cell proliferation increased and no alteration in apoptosis was detected [52]. Matthews et al. also reported the beneficial effects of pro-angiogenic VEGF overexpression on TESI formation, by means of an inducible, ubiquitous genetic system. Overall, OUs overexpressing VEGF formed TESI that grew faster and bigger after 4 weeks in vivo when compared to control, also presenting higher villi and deeper crypts with all differentiated cell types. CD31/PECAM staining proved that capillary density and crypt epithelial cell proliferation were also increased in the overexpressing TESI [53].

Growing the tissue-engineered small intestine from organoid units on a scaffold requires that ISCs be co-isolated with cell members of the niche that regulate the balance of renewal and differentiation of the resident stem cells. Wnt is a family of highly conserved, secreted signaling proteins that play a crucial role in development and stem cell proliferation control, maintenance, and differentiation in the adult vertebrate, including ISCs [54]. Wnt is palmitoylated in the ER by Porcupine and secreted with the assistance of Wntless/Evi in the Golgi and plasma membrane. It then diffuses through the ECM and acts upon target cells expressing the seven-pass transmembrane receptor Frizzled and its adjacent Lrp5/6 (low-density lipoprotein receptor-related protein) co-receptors [55]. The third element involved in Wnt recognition by ISCs is the Lgr5 receptor. It is likely that targeting Wnt isoforms could be beneficial for the crypt intestinal stem cell niche and other Wnt-responsive organs. Indeed, drug candidates that enhance and especially those that block Wnt signaling have been studied in diseases, such as various types of cancer, Alzheimer's disease, osteoporosis, fracture repair, and ES/iPS stem cell differentiation. However, this pathway still poses several challenges as a therapeutic target. So far, 19 Wnt ligands and 10 Frizzled receptor isoforms are known, rendering specificity and control of individual downstream events a real

challenge for a biopharmaceutical approach. Additionally, short pulses of Wnt are known to be sufficient for developmental steps in the embryo, implying that long exposures to Wnt are unnecessary and that a rigorous control of this signaling protein will be required [56]. Finally, many cell targets are susceptible to Wnt, increasing possible off-target responses and restraining its use for in vitro and animal models. Consequently, an approach that enhances the beneficial downstream effects of endogenous Wnt without generally altering the total Wnt input through a co-mediator might be better suited for therapy. R-spondins belong to a thrombospondin type-1 repeat (TSR-1)-containing protein superfamily. The R-spondin members (Rspo1–4) also bear positively charged amino acids at the C-terminal region, and two cysteine-rich, furin-like domains at the N-terminus, which are necessary and sufficient for Wnt signal potentialization. Lgr receptors (Lgr4, −5, and −6), which physically interact with Lrp5/6 and Frizzleds, have recently been identified as receptors for all four R-spondins [57–59]. In particular, intestinal Lgr5+ (stem) cells at the base of the crypt respond to Rspo1 by becoming highly proliferative. Rspo1 also acts as an in vivo mitogenic growth factor for the intestinal epithelium in the mouse [57, 60], allowing for expansion of epithelial mass in culture systems. Thereby, R-Spondins may improve the way TESI develops and is a potential molecule for clinical use in the future.

The fibroblast growth factor (FGF) family comprises a set of over 20 heparin-binding proteins in humans. FGFs regulate cell differentiation, proliferation, migration, and survival and display broad angiogenic and mitogenic activity, being required in the development of multiple organs, including those of the gastrointestinal tract [46, 61–63]. Among FGF members, FGF10 has been implicated in dysgenesis of digestive organs when ablated (Fgf10−/−) [62]. Conversely, Tai et al. were the first to provide evidence that FGF10 overexpression in the ileal crypt epithelial assists intestinal adaptation following massive small bowel resection [64]. A 2013 report by Torashima et al. has now proven that this protein is also helpful in the formation of tissue-engineered small intestine [65]. With overexpression of FGF10 in organoid units implanted in host animals under doxycycline administration to activate the transgene, results were obtained that were similar to the approach of direct VEGF overexpression [53]. TESI size and weight were augmented and higher villi and deeper crypts were obtained. Also, the proliferation of crypt epithelial cells was enhanced, and terminal cell differentiation was not compromised [65].

In view of the crucial role played by peptide growth factors and hormones not only in embryonic development and several physiological processes but also in tissue engineering, scientists have systematically pursued in vitro production of their recombinant human counterparts. Over the past decade, there has been heterologous expression in bacteria, mammalian, and insect cells of a number of these recombinant factors/biopharmaceuticals, namely, human prolactin, amylin, FGF, PDGF, VEGFs, G- and GM-CSFs, TGF-beta 1 and 3, and BMPs 2, 4, and 7.

Conclusion and Future Perspectives

Patients suffering from intestinal failure, as in short bowel syndrome, are still in need of a better alternative for their condition to overcome high morbidity and mortality rates. Tissue engineering techniques have improved considerably over the last two decades and may bring a gold standard substitute to the currently available therapies, including transplantation. Autologous tissue-engineered intestine is one promising solution. Preserving the stem cell niche and the surrounding mesenchyme appears to be important and may be critical for the maintenance of signaling pathways. But additional biological factors may also be necessary. Indeed, several reports have demonstrated the beneficial effects of adding growth factors, such as GLP-2, FGF10, and VEGF, to the organoid unit-scaffold construct in animal models, but choosing the best candidates is the next challenge. Also, many promising candidates, such as R-Spondins, still need to be included in these investigations. Further studies should focus on refinement of the spatiotemporal

delivery of peptide factors, which is dependent on dose, stability, and the number of biologicals being delivered at once, and further understanding of the interaction of these molecules with synthetic and organic scaffolds. These strategies are likely to accelerate the successful development of the regenerating intestine, for the goal of a future human therapy to improve the lives of patients who greatly depend on these discoveries.

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Distraction Enterogenesis

13

Farokh R. Demehri and Daniel H. Teitelbaum

Abbreviations

DFM	Dilating fenestrated elastic mask
ERK	Extracellular signal-related kinase
FAK	Focal adhesion kinase
GLP-2	Glucagon-like peptide 2
IGF	Insulin-like growth factor
MAPK	Mitogen-activated protein kinase
PN	Parenteral nutrition
PU	Perfusion unit
SBS	Short bowel syndrome
SEMS	Self-expanding metal stents
STEP	Serial transverse enteroplasty

Introduction

Short bowel syndrome (SBS) is a devastating disease that is associated with a high rate of morbidity and mortality rate exceeding 30 % [1]. An estimated 40,000 patients with intestinal dysfunction from SBS require parenteral nutrition [2]. Cost of care for SBS patients is in excess of $300,000 per patient per year, and estimated costs in the United States have exceeded $1 billion yearly [1]. A number of modalities have been used to treat SBS, including the use of growth factors, surgical lengthening of the small bowel, engineered constructs, and small bowel transplantation. Unfortunately, the results of these treatments have been disappointing with a high rate of complications and death. Recently, substantial work has demonstrated that mechanical forces can be powerful regulators of tissue growth or regeneration. Through the process of mechanotransduction (the translation of mechanical signals to biochemical ones which affect cell function [3]), the response to these forces results in a cascade of actions which alter cell-cell contact, cell adhesion, and activation of proliferative mechanisms [4, 5]. Numerous tissues and organs have been shown to be mechanoresponsive, including bone, lung, and neural tissue [3, 4]. The current chapter looks at the potential use of applying distracting forces in a linear fashion to small bowel in order to gain intestinal length – distraction enterogenesis.

Concept of Distraction Enterogenesis

Among the causes of intestinal failure outlined in this text, short bowel syndrome (SBS) remains the most common [6]. While significant advances have been made in the management of patients

F.R. Demehri, MD
Section of Pediatric Surgery, Department of Surgery, University of Michigan, Ann Arbor, MI, USA

D.H. Teitelbaum, MD (✉)
Section of Pediatric Surgery, Department of Surgery, University of Michigan, Ann Arbor, MI, USA

Section of Pediatric Surgery, Mott Children's Hospital, University of Michigan, 1540 E. Hospital Dr., SPC 4211, Ann Arbor, MI 48109-4211, USA
e-mail: dttlbm@umich.edu

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with SBS – including novel parenteral nutrition (PN) strategies, growth hormone therapy, and surgical lengthening – the fundamental deficit of reduced intestinal absorptive capacity remains, leaving many patients chronically dependent on parenteral nutrition. The significant complications of prolonged PN dependence in the setting of SBS – including metabolic abnormalities, hepatic dysfunction, and sepsis – contribute to the considerable morbidity and mortality that remain for patients with this disease [7–10].

The underlying etiology of SBS is a critical loss of intestinal length, resulting in a loss of functional intestinal surface area with subsequent inadequate absorption of nutrients and water. The remarkable progress in supporting patients with SBS has largely been due to improved compensation for this lack of intestinal length – either via alternative nutrient delivery (i.e., PN), enhanced mucosal turnover (i.e., glucagon-like peptide 2 [GLP-2] analogue therapy), or surgical tapering to increase the course of transit of nutrients through a given segment of intestine (i.e., serial transverse enteroplasty [STEP]). These interventions do not directly address the lack of intestinal length, however. The most significant predictor of the ability of a patient to wean off of PN support is the patient's residual small bowel length [7–9, 11]. This may explain the number of patients who remain PN dependent, despite maximum medical and surgical therapy.

In this chapter, we introduce distraction enterogenesis, a novel approach under development to treat SBS. Distraction enterogenesis is the use of applied mechanical force to induce intestinal elongation. It was first described in 1994 by Printz et al. using a rabbit model [12]. In this model, a segment of jejunum was brought to the abdominal wall as blind-end jejunostomy, through which an extracorporeal screw was inserted. Advancement of this screw by 1 mm/day achieved a doubling of the intestinal length within 3 weeks. Subsequent studies using more refined distraction techniques in larger animal models have established distraction enterogenesis as a reproducible phenomenon with the potential to achieve clinically significant intestinal lengthening [13–17]. Importantly, the multifold lengthening achieved with distraction enterogenesis preserved intestinal function, with sustained lengthening after completion of the distraction process [16, 18, 19]. While it has yet to be studied in humans, ongoing advances have brought this approach close to becoming a clinical reality.

Mechanotransduction: Mechanism of Action

The principle of distraction enterogenesis finds parallels in other clinical contexts, where mechanical force has been long used to induce tissue growth. For example, soft tissue expanders have been used for decades to induce skin growth via gradual tension [20, 21]. Similarly, the use of longitudinal traction is an effective method of increasing bone length via distraction osteogenesis [22]. These applications harness the phenomenon of mechanotransduction, wherein a mechanical force induces tissue growth [23, 24]. When tension is applied to tissue with replicative potential, mechanotransductive signaling leads to increased cellular proliferation and subsequent tissue growth in the axis of tension application [5]. Other examples of clinically established mechanotransductive tissue lengthening include vascular [25] and esophageal lengthening [26].

One bridge between the extracellular matrix and cell is surface integrins (e.g., alpha V, beta 1). These integrins can subsequently activate (via phosphoinositol 3-kinase [27]) and a number of intracellular processes which can secondarily mediate cellular proliferation and growth [28]. These factors include adjacent sub-cell membrane members of the c-src family and focal adhesion kinase (FAK) [29]. Activation of such factors may be manifested by either the increased expression of these factors (e.g., FAK) [4] or phosphorylation (activation) of FAK [28, 30]. Activation of the mitogen-activated protein kinase family (MAPK) with eventual extracellular signal-related kinase (ERK1/2) activation [29] appears to be a final path resulting in cellular proliferation. Activation of transcription factors can mediate proliferation, either independently

or dependently on a number of growth factors (e.g., c-fos and IGF-I) [31]. FAK and other submembrane factors (e.g., paxillin) also translate mechanical signals to the nucleus via the Rho family and actin intracellular filaments [5, 32].

We have recently explored the mechanisms of enterogenesis using a mouse model using a closed loop of small bowel filled with a hypertonic solution [16, 18]. Using untargeted (two-dimensional gel electrophoresis) and known targeted pathways (e.g., FAK), we identified that many of the classically defined pathways in other organs driven by mechanotransduction mechanisms were also seen in the small bowel. A summary is shown in Fig. 13.1. Physical force (potentially via cell membrane integrins) drives the FAK pathway which plays a central role in mechanotransduction during enterogenesis. FAK activation leads to polymerization with α-actinin. Beyond the mechanisms shown in Fig. 13.1, this polymerization leads to several downstream regulatory processes, including RAC-1 and cell shape changes. RAC has been shown to activate p38 MAPK which can lead to p-Akt activation and decreased apoptosis. FAK activation also led to Akt and ERK activation facilitating proliferation and survival. Whether the cell shape change and the increase in cell proliferation and survival are directly linked remains to be addressed.

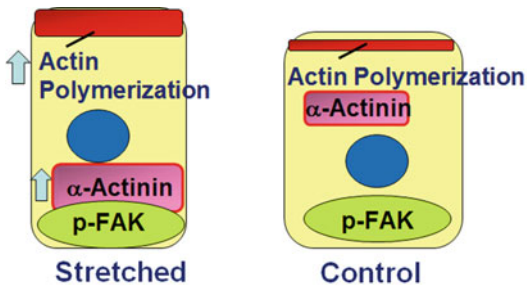

Fig. 13.1 Potential model of mechanotransduction forces driving enterogenesis. Physical force drives the activation of the FAK pathway (via phosphorylation) which has a central role in mechanotransduction during enterogenesis. FAK activation leads to a polymerization with α-actinin. This then leads to several downstream regulatory processes, including RAC-1 and cell shape changes. Although not shown in the figure, RAC has been shown to activate p38 MAPK which can lead to p-Akt activation and decreased apoptosis. FAK activation also led ERK activation facilitating cell proliferation and survival. Whether the cell shape change and the increase in cell proliferation and survival are directly linked remains to be addressed

Enterogenesis Leads to Normal Intestinal Function and Morphology

A critical question is whether bowel which undergoes lengthening retains normal function, including nutrient absorption, motility, and morphology. Using a rat model, investigators have shown intestinal mucosal digestive enzymes are retained including a number of disaccharidases and alkaline phosphatase [33, 34]. More recently, using this same rat model, the Dunn laboratory has shown preserved motility.

Reimplantation of the bowel into the normal continuity consistently showed improvement of GI function. Certainly, enteric flow can lead to dramatic improvements in GI function, and this included glucose absorption and peristalsis [19]. This same restoration of continuity was also found with neuroganglion cells, a critical system for normal motility. During the process of lengthening, numbers of ganglia declined, but after restoration of bowel continuity, the number reached control levels [35].

Using a pig model of enterogenesis, Koga et al. demonstrated similar findings to those previously mentioned [18]. Several key points were shown. First, and most importantly, upon reimplantation of the lengthened segment in this large animal model, the gained length persisted. Second, nutrient absorption, epithelial barrier function, and motility (including transit time) were similar to control segments. Finally, pigs thrived and gained weight after reimplantation, supporting this as a clinically viable approach.

Enterogenesis Leads to Growth of the Entire Thickness of the Bowel Wall and Its Vascular Mesentery

The demonstration of the growth of the myenteric plexus distribution during the period of enterogenesis suggests that the entire intestine

wall grows. In fact, the muscularis propria significantly increases in thickness during enterogenesis [16, 19]. Using a more clinically relevant pig model and three-dimensional imaging of the vasculature, the mesenteric vessels actually increase in their branching pattern and overall volume, suggesting that enterogenesis is driving increased blood flow to the growing bowel [36].

Clinically Relevant Distraction Enterogenesis Device Approaches

Prior distraction enterogenesis device approaches have required the surgical creation of blind-ending intestinal segments [13, 14] or the placement of transmural sutures or circumferential vessel loops [37, 38]. These intestinal attachment approaches all require open surgical device placement and reoperation for removal and restoration of intestinal continuity. This unfortunately has led to significant intestinal length loss, increases the risk of surgery-related injury to the intestine, and adds considerable risk given the elevated systemic inflammatory response of SBS patients to laparotomy [39, 40]. Other approaches have included the use of novel expandable polymers in isolated segments [19]. Another recently described approach has been the use of an expandable shape memory alloy which stretches the bowel on the serosal surface [17], which would also require surgical device placement and removal. While no approach has achieved clinical utility to date, we will focus on the details of endoluminal distraction enterogenesis. This approach, wherein a device applies reversible longitudinal force to the intestine from within the bowel lumen, has the promise of allowing enterogenesis in a minimally invasive fashion.

Our group has taken a unique approach to create a method of distraction enterogenesis using a fully endoluminal intestinal lengthening device. The endoluminal approach to distraction enterogenesis remains an attractive strategy, as it would allow the application of distractive force using a device that may be placed via a stoma (e.g., gastrostomy or jejunostomy) or trans-orally. This may obviate the need for multiple operations. Attempts to employ a fully endoluminal distraction, however, have been limited by the lack of effective endoluminal device attachment, with atraumatic balloon-based approaches failing to provide the attachment strength required for enterogenesis [41]. Other strategies such as self-expanding metal stents (SEMS), while relatively safe for prolonged implant, are designed to be not readily detached [42]. In addition, SEMS are not designed to withstand high longitudinal force required for distraction enterogenesis. Further, because of their hourglass shape which grasps the bowel at both ends, there may be a high likelihood of perforation with an applied distractive force.

We began with the use of a double-balloon catheter design, similar to the approach taken for double-balloon enteroscopy. The device created distractive forces as the distance between the inflated balloons increased. A major limitation of this approach was insufficient device attachment to the inner lumen of the bowel wall. Further, if the balloon pressure increased excessively, it would induce ischemia [41]. To overcome this problem, we recently developed a novel expandable mesh attachment. This attachment design provided high-strength, reversible coupling of an endoluminal device within a compliant tube – the small intestine. With expansion, a high-friction mesh coated balloon allowed the application of over 500gf of longitudinal distraction without slip, well exceeding loads that have previously produced intestinal lengthening [41]. Given the high compliance of the small intestine, however, device uncoupling failed to occur with balloon deflation using a simple high-friction balloon, still requiring excessive tension of 200gf to slip. This would make device implantation and removal difficult and exceeds the safe upper limit of distraction before perfusion compromise as previously shown [43]. By covering the high-friction mesh with a novel dilating fenestrated elastic mask (DFM) attachment ensures separation of the compliant bowel wall from the attachment surface, uncoupling the device and reducing the tension required to slip to a safe 80gf. The current design of the device is hydraulically driven using a concentric piston device (Fig. 13.2) as previously described [36] and

adapted for linear actuation and inclusion of our DFM attachment.

Based on a series of preclinical implantations in 30–35 kg pigs, several key findings are noted below and are summarized in Fig. 13.3.

Lengthening: After 7 days of distraction, the cumulative percent growth of the bowel in contact with the device relative to fed control was 44 ± 2 % (Fig. 13.3a). The net gain in length is dependent upon the length of bowel which is exposed to distractive force, with notable variation in the percent length gain achieved at different points along the device. Therefore, the cumulative distance from the stoma to each marker along the distracted segment was measured and compared to the group of fed control segment marker intervals at explant. This was extrapolated over the same number of markers [41], yielding a total increase in length of 7.1 ± 0.3 cm vs. fed control. The increase in length exceeded the 1.1 cm stroke length of the device, indicating multiple payout distraction. This degree of lengthening is actually quite comparable to the current gold-standard surgical lengthening procedure of a primary STEP procedure, which produces between 22 and 43 % bowel lengthening per operation [45–47]. While bowel lengthening operations such as STEP create length gains at a single setting, however, distraction enterogenesis produces lengthening over the period of time during which distraction is applied. Therefore, results were measured relative to control bowel after the same period rather than comparing to the same segment of intestine at the time of device implant.

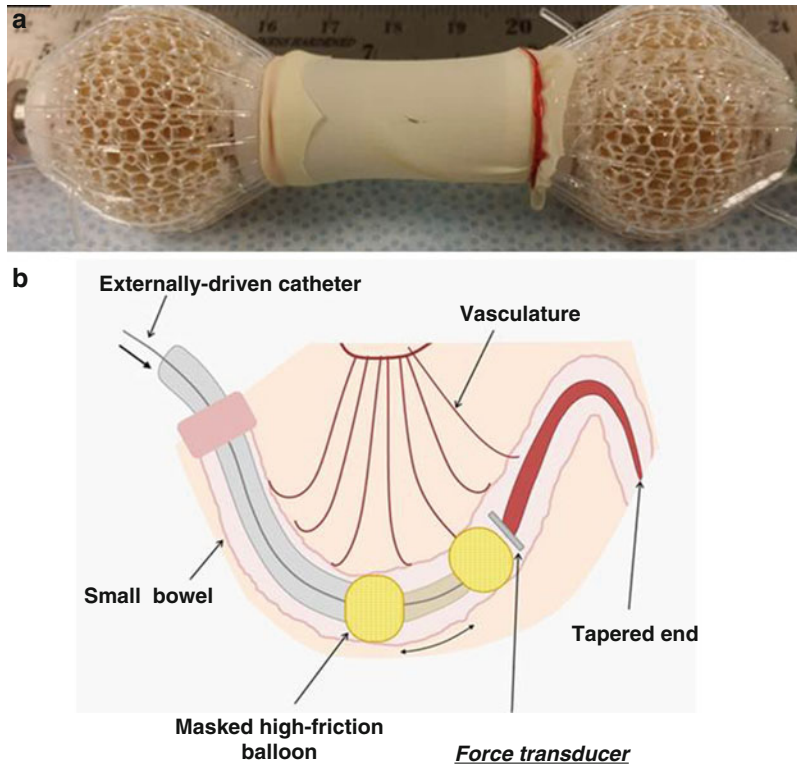

Fig. 13.2 Current preclinical endoluminal device design. (**a**) Close-up view of the dilating fenestrated elastic mask (DFM attachment). (**b**) Schematic drawing of the preclinical design. Note the two DFM balloons (labeled masked high-friction balloons); the external drive applies a hydraulic distracting load between the balloons after they attach to the inner lumen of the bowel wall. To ensure accurate measurement of distractive forces, a force transducer is placed at one end of the device. Finally, to avoid forces distal to the device which could lead to a perforation, a geometric tapered end is used, as previously described [44]

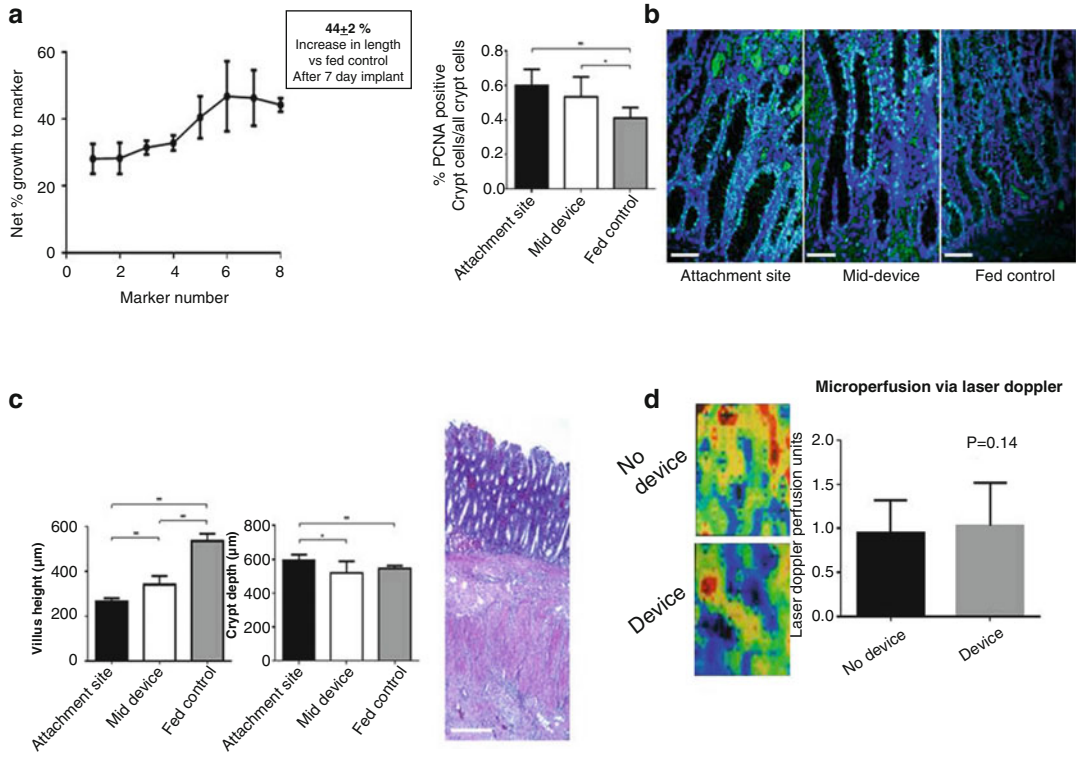

Fig. 13.3 Preclinical outcomes of MEND derived from 35 kg Yorkshire pigs. (**a**) Overall gain in length after a 7-day period of distraction. (**b**) Intestinal epithelial cell proliferation, using PCNA staining, demonstrates a significant increase in proliferation. (**c**) Histologic inspection of the mucosa failed to show any mucosal disruption. (**d**) Laser Doppler scanning failed to show any loss of blood flow in the implanted area of the bowel during the application of distractive forces

Epithelial cell proliferation: PCNA staining of unfed distracted bowel (mid-device) without attachment contact demonstrated increased epithelial cell proliferation vs. fed control (53.4 ± 11.5 % vs. 41.0 ± 6.2 %; p = 0.04; Fig. 13.3b). Attachment sites similarly demonstrated an elevated proliferative index vs. fed control (60.0 ± 9.4 %; $p < 0.01$), though not significantly greater than mid-device bowel ($p = 0.26$).

Histologic changes: Histologic examination of attachment sites demonstrated loss of villus height (265.3 ± 15.7 μm) compared to fed control (535.2 ± 33.4 μm; $p < 0.01$) and mid-device bowel (341.3 ± 38.6 μm; $p < 0.01$; Fig. 13.3c). Attachment site crypt depth was increased (594.3 ± 33.1 μm) vs. fed control (546.3 ± 15.8 μm; $p = 0.01$) and mid-device bowel (519.7 ± 68.4 μm; $p = 0.04$). Muscularis mucosa thickness increased at attachment sites (57.7 ± 6.3 μm) vs. fed control (41.3 ± 9.4 μm; $p < 0.01$) and mid-device bowel (40.9 ± 6.0 μm; $p < 0.01$). On the other hand, muscularis propria thickness was not significantly different between the attachment sites (534.2 ± 37.4 μm), fed control (559.0 ± 16.9 μm; $p = 0.17$), and mid-device bowel (551.0 ± 20.1 μm; $p = 0.36$).

Device safety: Laser Doppler (Fig. 13.3d) assessment demonstrated no significant decrease in intestinal tissue perfusion with the DFM attachment (0.21 ± 0.07 perfusion units [PU] vs. 0.30 ± 0.09 PU; inflation vs. deflation; $p = 0.46$). PU is a dimensionless unit used for laser Doppler measurement. After 7 days of distraction, no device-related intestinal obstruction, perforation, or anastomotic complication occurred. Gross inspection of the mucosa at attachment sites remained intact without ulceration.

Future Directions

Who Would Be the Ideal Patient for Distraction Enterogenesis Therapy?

One of the key challenges in pediatric SBS is that once a child is beyond the first 3–4 years after the diagnosis of SBS, their chances of weaning off of PN is quite low [6]. Thus, a realistic expectation would be that intervention between 3 and 4 years post-diagnosis would make the most sense, as the adaptive capacity of residual bowel has likely been exhausted at this point, requiring more aggressive therapy such as distraction enterogenesis. As efficacy data is accumulated for distraction enterogenesis, however, earlier implementation of this strategy may prove more useful. For example, a patient newly diagnosed with SBS who satisfies certain prognostic criteria making weaning off PN unlikely may benefit from early distraction therapy to increase residual small bowel length.

Previous studies have demonstrated that small bowel length predicts successful weaning from PN [7, 9, 48]. Of those patients who eventually achieve enteral autonomy, the majority do so within the first year. Predicting enteral autonomy in this high-risk group is particularly important, as these are the patients, if they fail to wean off of PN, who are most likely to experience long-term complications [7]. Given the relative infrequency of SBS, most previous series have been limited in patient volume, preventing subset analysis of chronically PN-dependent patients. In a recent study by our group and others, we identified that the percent small bowel which the SBS child has is a key predictive factor to successfully wean off PN [9]. The data shown in Fig. 13.4 demonstrates a key principal that those SBS children with longer lengths of small bowel have a significantly greater chance to wean off of PN. This supports a key premise that if we can increase the length of small bowel, we can improve the rate of enteral autonomy.

Finally, while no glucagon-derived peptide-2 (GLP-2) derivative has been approved for children, the use of distraction enterogenesis in combination with GLP-2 may prove useful in the future, as the addition in a mouse model has demonstrated some benefit in augmenting lengthening of the small bowel [49].

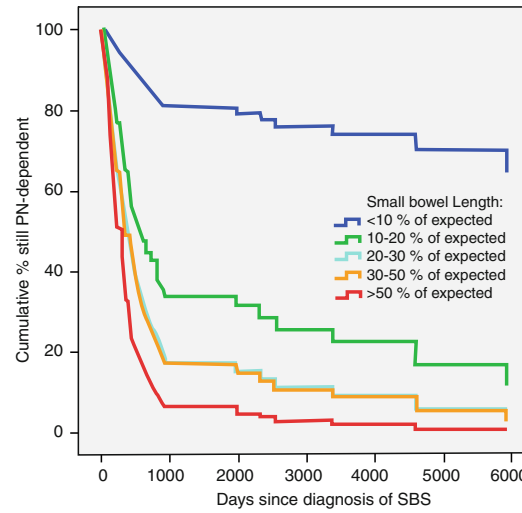

Fig. 13.4 Outcomes of 230 SBS children, demonstrating that the success of weaning off of PN increases with each 10 % increment in small bowel length [9]

Conclusion

Distraction enterogenesis techniques remain under development, with several device-based approaches showing promise in animal models. The central thesis of distraction enterogenesis – that controlled longitudinal tension application leads to durable increases in functional intestinal length – opens the door to new treatments for SBS. It remains to be seen how this approach will fit into future SBS treatment paradigms, but with continued refinement and clinical study, distraction enterogenesis may emerge as a key treatment modality for reversing SBS.

Conflicts of Interest The authors declare no conflicts of interest.

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