Nutritional Support in Paediatric Patients (1) Topic 4

Module 4.3

Nutrition Treatment in Children with Intestinal Failure with a Special Emphasis on Short Bowel Syndrome

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Learning Objectives

- To define chronic intestinal failure (IF) and its aetiology with respect to different age groups;
- To discuss pathogenesis of intestinal failure with a special emphasis on the short bowel syndrome (SBS) and on its major prognostic determinants in children;
- To define intestinal adaptation and to present factors promoting it;
- To describe various stages in clinical presentation with particular attention to changes in nutritional requirements;
- To present treatment options with respect to nutrition support, medical treatment and surgery;
- To present basic concepts of enteral nutrition and to describe administration of feed with respect to formula composition, sites, routes and modes of delivery;
- To discuss parenteral nutrition in children with intestinal failure with respect to venous access, composition of parenteral nutrition and prevention of major complications of long-term parenteral nutrition such as central venous catheter (CVC) associated bloodstream infections, and intestinal failure associated liver disease (IFALD);
- To provide an overview of the current concepts of medical treatment, particularly with respect to possibilities of improving intestinal adaptation;
- To discuss surgical options for bowel reconstruction, and indications for intestinal transplantation in patients with SBS;
- To define an intestinal rehabilitation programme and discuss its benefits;
- To present benefits and principles of home parenteral nutrition and the multidisciplinary team approach.

Contents

Key Messages

- IF results from a reduction in the functional gut mass below the minimum required for absorption of water and nutrients to maintain weight on oral/enteral intake in adults, and to sustain growth in children;
- Short bowel syndrome, which develops after massive surgical resection, is the commonest cause of IF in children, followed by intractable diarrhoea due to congenital defects in intestinal transport and digestion, and then by severe motility disorders;
- The severity of the clinical presentation and the prognosis for intestinal adaptation, which invariably follows resection, depend on the length, type and functional integrity of the residual bowel, on the presence of ileocaecal valve and the colon, and the age when the resection was performed;
- The presence of food in the gut is the most important factor promoting bowel adaptation, notably intestinal hyperplasia and hypertrophy. Food is introduced in small, trophic amounts as soon as possible, and advanced to the maximal volume and concentration tolerated without worsening of the clinical presentation, while avoiding overfeeding. Breast milk is the best enteral/oral feeding option for babies;
- The use of PN is implicit in all patients with IF; some of them will require life-long PN. Therefore, prevention of its complications such as CVC-related bloodstream infections, loss of venous access, IFALD and inappropriate growth, cannot be overemphasised. Strict adherence to aseptic procedures during CVC insertion and its subsequent maintenance, cyclical PN at home and the multidisciplinary team approach within structured intestinal rehabilitation programmes are among the most important preventive measures;
- Intestinal transplantation is a life-saving procedure reserved for patients who have failed to achieve enteral autonomy, and at the same time have developed life-threatening complications;

- Centralized multidisciplinary health care, in institutions with well-developed intestinal rehabilitation programmes under the surveillance of expert teams, has resulted in significantly improved morbidity and lowered mortality of children with IF.

1. Intestinal Failure (IF) Definition and Aetiopathogenesis

1.1 Definition of IF

IF is a condition of severe intestinal malabsorption due to a reduction of the functional gut mass below the minimum needed to absorb nutrients and fluids required to maintain weight on oral intake in adults, and to sustain age-appropriate growth in children (1). Therefore, all patients with IF require parenteral nutrition (PN) in various amounts and for different periods of time. Moreover, the percentage of fluid and nutritional requirements that need to be covered via the parenteral route are, in clinical practice, the best indicator of the degree of the intestinal sufficiency (2). Very recently the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) defined IF as the need for parenteral nutrition (PN) for >60 days due to intestinal disease, dysfunction, or resection (3). Estimates of prevalence vary greatly as there is no internationally agreed definition; based on registry data, a point prevalence in the UK was 13.7 per 1,000,000 children in 2011 (4), in a Dutch paediatric population it was 9.5 (5), and in Italy it was 14.12 per 1,000,000 inhabitants younger than 19 years (6).

1.2 Aetiology of IF (Table 1)

The aetiology of IF in developed countries can be divided into three broad groups:

a. **Short bowel syndrome (SBS)** is defined as chronic IF due to massive gut resection resulting in severely impaired ability to absorb water, electrolytes and nutrients to an extent whereby PN becomes a prerequisite for life. A definition proposed recently by the NASPGHAN is the need for PN for >60 days after intestinal resection, or a bowel length of <25% of expected (3). Of all paediatric SBS, 80% occurs during the neonatal period, with an incidence of 0.7% and 1.1% among very low and extremely low birth weight neonates in the USA (7). In the paediatric population the incidence is approximately 20-30 per 100,000 live births per year (8). Conditions leading to extensive surgical resection are age dependent and are presented in **Table 1**.
b. **Severe enteropathies** are most commonly caused by congenital enterocyte defects resulting in intractable diarrhoea. They are rare disorders of nutrient and electrolyte transport or digestion defects, or defects in enterocyte differentiation and polarization. The most common among them are microvillus inclusion disease, tufting enteropathy, syndromic diarrhoea and autoimmune enteropathy.
c. **Intestinal motility disorders** affect either the enteric nervous system or intestinal smooth muscle. They are a heterogeneous group of diseases, but the most severe forms causing chronic IF are present already at birth, such as long segment colonic and intestinal aganglionosis (Hirschsprung's disease) and chronic intestinal pseudo-obstruction (CIPO).

Considering all three groups, the most frequent cause of IF is SBS (50% - 60%) which will therefore be described in more detail, followed by congenital enteropathies (30% - 41%) and the intestinal motility disorders (5% - 9%) (9).

Table 1
Conditions leading to SBS with respect to age

PRENATAL	INFANTS	OLDER CHILDREN & ADULTS
Defects of abdominal Wall Multiple atresia Volvulus Extensive aganglionosis Motility disorders	Necrotising enterocolitis Meconium ileus Volvulus Invagination Vascular accidents Motility disorders	Vascular accidents – infarctions Crohn's disease Radiation enteritis Polyposis syndromes Trauma, Tumours Jejunoileal bypass in obesity

1.3 Pathogenic / Prognostic Dterminants of IF/SBS (Table 2)

Length of the residual bowel. The length of the residual bowel has been historically recognized as the most important prognostic factor. However, there are many other relevant variables influencing the ultimate adaptation of the bowel and the prognosis of the IF. For example, during the third trimester of intrauterine life exceptionally rapid intestinal growth occurs, and the small intestinal length increases by nearly 150%. This rapid growth continues postnatally, and the small bowel doubles again in the first 18 months of life. Therefore, the earlier in life resection occurs – for example in preterm babies - the better the potential for adaptive intestinal growth. At term, neonates have a small intestinal length of some 230-250 cm. In general, severe SBS will develop if less than 40 cm of the viable small bowel is left. Nevertheless, due to an enormous adaptive capacity of the small intestine (see later), life without PN has been described with as little as 15-30 cm of residual small intestine (reviewed in 3, 10, 11).

The type of the residual bowel seems to be particularly relevant for IF development. The basic features of jejunal mucosa are longer villi, higher concentrations of enzymes and of transport proteins, and therefore the majority of nutrients are rapidly absorbed here. However, the tight junctions are leaky, affecting the ability of the jejunum to absorb electrolytes and water against the concentration gradient, and allow maintenance of the intraluminal sodium concentration at around 90-100 mmol/L. Consequently, if jejunum is left without ileum and/or colon, huge amounts of water and electrolytes will be lost. The ileal mucosa is tighter, allowing better absorption of salt and water. Moreover, in the terminal ileum there are specific transport mechanisms for bile acids and vitamin B12 that cannot be undertaken by any other segment of the bowel. Finally, the ileum can adapt and absorb the majority of nutrients that escape from the jejunum, and due to the "ileal brake" presence of fat in the ileum will slow down the transit in the remaining GIT. The colon is an important site for water and electrolyte absorption and it is also capable of salvaging some 20-40 g of carbohydrates that have escaped small bowel absorption.

The ileocaecal valve (ICV) slows down intestinal transport and helps to prevent small bowel bacterial overgrowth with microorganisms originating from colon. Previously, its presence was considered as an important beneficial prognostic determinant. However, recent studies have not uniformly confirmed this important role of the ICV (reviewed in 12).

Integrity of the residual bowel. One of the most important prognostic determinants in IF is the functional status of the residual bowel. In the case of the primary motility disorders, congenital enteropathies, Crohn's Disease or postradiation enteritis, dysfunctional residual bowel will significantly diminish the possibility of achieving enteral autonomy through

intestinal adaptation. In a recent analysis of infants with short bowel syndrome the most important predictors of enteral autonomy were the percent of the residual small bowel and the length of colon in continuity, while septic episodes had a negative impact (13). Other factors associated with an increased likelihood of weaning from parenteral nutrition (PN) were normal bowel motility, lack of intestinal dilation, and care at a rehabilitation centre (10, 14).

Table 2
Prognostic determinants of IF caused by SBS (13, 53)

Positive	Negative
Ileum as the residual segment	Jejunum as the residual segment
ICV and colon in continuity	High jejunostomy
Early age at resection	Resection after the age of 2y
"Healthy" residual gut	Dysfunctional residual segment
Care at intestinal rehabilitation centre	Pseudo-obstruction, enteropathy

1.4 Intestinal Adaptation (Table 3)

The term intestinal adaptation applies to the progressive recovery in functional gut mass which occurs following resection through a combination of mucosal hypertrophy and hyperplasia. Moreover, increased quantities of enzymes and transport proteins result in more efficient digestion and absorption per unit of the remaining mucosal surface (15). Adaptation starts as early as 24 hours after resection and continues for 12-18 months in adults and into 5th year if the resection occurred at an early age (preterm babies) (16). Ultimately, at the end of the adaptive period 90-100 cm of the small intestine is required to sustain life and growth on enteral intake, provided that the colon is in continuity, and that the remaining gut is functionally intact. Numerous factors that could beneficially affect adaptation are listed in **Table 3**, but the single most important driving force, setting into motion all other potentially beneficial variables such as bile, pancreatic enzymes, vascular supply, propulsive motility, etc., is the presence of food in the bowel lumen. Enteral/oral feeding is therefore the key issue in the promotion of intestinal adaptation, and consequently in the prognosis of IF due to SBS.

The most widely evaluated pro-adaptive agents used in humans are growth hormone, endothelial growth factor, glutamine, insulin and glucagon-like peptide 2 (GLP-2); their effects have been recently summarized by Weih S et al (17). However, the latest trials have substantially reduced the enthusiasm for growth hormone and glutamine. GLP-2 remains promising, albeit with very high costs for the clinically usable analogue teduglutide, which currently limits its use. The native hormone is produced by the L-cells of the terminal ileum and colon in response to luminal nutrients and has a pro-adaptive effect with the net increase in the digestion and absorption. Patients with resection of the ileum and colon and subsequent low levels of the GLP-2 could be the best candidates for this treatment option (10, 11, 18).

Table 3
Factors with positive effect on intestinal adaptation (17, 53)

Presence of food in the intestinal lumen through improvement of - vascular supply - secretion of gut hormones, peptides & enzymes - propulsive motility - gallbladder emptying
Endothelial growth factor
Growth hormone
Insulin
Glutamine
Glucagon-like peptide 2 and its analogues

1.5 Clinical Presentation of the SBS & General Concepts of Nutrition Treatment (Table 4)

The clinical presentation of children with SBS can be divided into 3 different phases which are important to acknowledge as they have significant implications on the treatment, particularly with respect to nutrition therapy:
a. in the *early phase* water and electrolyte losses, the severity of which depend on the surface loss and on the type of the bowel resected (see above), can cause rapid dehydration and electrolyte imbalances;
b. in the *intermediate phase* a malabsorption syndrome develops with the loss of almost all nutrients, in particular water, fats and fat soluble vitamins; as adaptation takes place malabsorption diminishes, the patient stabilizes, enteral intake can be increased and the PN requirements subsequently decrease;
c. the third *late phase* is a steady state reached after maximal bowel adaptation has been achieved. In this late phase, with respect to nutritional requirements and feeding techniques, patients with SBS may present with: a. complete or partial dependence on PN with development of various side effects of i.v. nutrition; b. continuing enteral nutrition, most commonly during the night; c. nutritional deficiencies requiring dietary adjustments and supplementations. Various complications, most commonly developing in the late phase of SBS, are presented in **Table 4**.

Different dietetic modalities, adjusted to the clinical stage of the IF in general, and to SBS in particular, with an individualized approach to each paediatric patient with respect to the nutritional requirements, are therefore the main pillars of treatment. Nutrition treatment begins with i.v. rehydration and supplementation of electrolytes and minerals to cover the requirements and the ongoing losses, followed by the introduction of PN. As early as possible EN is also to be introduced – at the beginning in minimal amounts just to provide a trophic role. Further on, the ratio between EN and PN should be continually adjusted to the patient's increasing absorptive and digestive capacities. In parallel with the intestinal adaptation, PN requirements will gradually diminish and it will become possible to increase the enteral intake.

Table 4
Complications / disorders associated with IF and SBS (53)

- Poor growth
- Food allergy
- Metabolic disorders:
  - acidosis, D-lactic acidosis
  - water and electrolyte disorders
- Distended poorly mobile residual bowel can cause / aggravate:
  - pseudo-obstruction
  - small bowel bacterial overgrowth
  - bacterial translocation, sepsis
  - secretory and osmotic diarrhoea
  - cholestasis,
  - liver fibrosis
- Other intestinal complications:
  - stenosis and obstruction
  - prolapse, stenosis and infection of stomas
- Peptic diseases:
  - ulcers in stomach / duodenum and at anastomoses
  - gastro-oesophageal reflux
- Nephropathy:
  - hyperoxaluria
  - kidney stones
  - kidney failure
- Metabolic bone disease
- Venous access complications resulting in loss of venous access:
  - central venous catheter related sepsis
  - obstruction or dislocation of, or damage to the catheter
  - thrombosis
- Liver disease:
  - IFALD
  - gallstones, cholecystitis, biliary sludge
- Psychosocial problems:
  - food aversion
  - hospitalisation
  - family relationship problems

2. Enteral Nutrition (EN) & Oral Feeds

2.1 Basic Concepts

EN is defined here as providing nutrients into the gut irrespective of the route (oral, tube, stoma), and is considered as the best approach which should be used to the maximal amount tolerated by the residual gut. Presence of food in the intestine promotes intestinal adaptation thereby increasing the functional gut surface available for digestion and absorption, with a subsequent decrease in the requirements for PN. EN is a major stimulus for secretion of gut hormones and other peptides, resulting in the improvement of gut motility and gallbladder contractions, which is particularly important as stasis of both is implicated in the pathogenesis of IFALD (see later) (reviewed in 19). However, despite the obvious importance of EN for the ultimate prognosis of IF, there are very few randomized controlled trials and almost all recommendations are based on expert opinion and consensus statements. Feeding should be initiated as soon as possible after the surgery, usually within

the first 24-36 hours, with a minimal volume (10-12 ml/kg/day) of diluted formula (if not breast-fed) to serve more as the source of trophic factors than as nutrition itself (20). The amount can be advanced every few days or in regular increments of 1 ml/hour/day, governed by water and electrolyte balance and clinical signs of nutrient malabsorption such as emesis, abdominal distension, high stool output, perianal/peristomal skin breakdown, weight loss, etc. (10, 20, 21). If the clinical picture deteriorates, a previously well tolerated volume and concentration should be reinstituted. This process may take many months and occasionally cannot be accomplished, in which case there is irreversible IF.

2.2 Type of EN

Breast milk is the best option with which to feed infants with IF as it contains high amounts of IgA, glutamine, LC-PUFAs, nucleotides and other components that could positively influence maturation of the infant immune system. There is very little evidence and scientific information on what to feed if breast milk is unavailable. A dilated residual small bowel segment could be accompanied by bacterial overgrowth and increased mucosal permeability, which increases the risk of cow's milk protein allergy. Some experts therefore recommend the use of an extensively hydrolysed formula, while others have found amino acid based formulae to be more efficient in decreasing PN requirements (22). It is reasonable to start with an elemental formula (amino-acid based), switching to extensively hydrolysed and then, if tolerated, to polymeric feeds, particularly if the patient is older than 1-2 years. In a recently published review enteral adaptation was not found to be significantly influenced by the type of the starting enteral diet (23).

2.3 EN Mode & Site & Route

The reduced absorptive surface and deficits in transport proteins may be more efficiently used, and the osmotic load of feeds is better tolerated if continuous EN is applied. However, intermitteTnt feeding provides cyclical hormonal surges and regular gallbladder emptying, and if delivered orally supports development of age-appropriate feeding habits and oromotor skills. Therefore continuous EN is preferable only shortly after surgery. Small oral bolus feedings during the daytime should be started as soon as possible as an adjunct to the night-time continuous mode of enteral feeding (19-24).
EN can be administrated either into the stomach or into the proximal small intestine, depending on: a) the morphological and functional status of the gut; b) the expected duration of EN; c) the anticipated risk of aspiration. Intragastric feeding is recommended whenever possible as it stimulates physiological digestive and hormonal responses, retains the antimicrobial properties of gastric juice, is associated with better toleration of hyperosmolar solutions, and because the stomach serves as a reservoir gradually releasing nutrients into the small bowel (25, 26). As the expected duration of EN in children with IF almost always exceeds 8-12 weeks, percutaneous endoscopic gastrostomy is the recommended route in a stable patient (27).

2.4 Oral Feeds & Nutrients with Special Beneficial Effects

Solid foods and oral feeds can be slowly introduced at the developmentally appropriate stages (summarized in 19). A high carbohydrate (50%-60% of energy) and low fat diet

(20%-30%) is often recommended in patients with the colon in continuity, while higher fats (30%-40% of energy) and lower carbohydrates (40% to 50%) may be preferable if the colon is absent (22). In the absence of the colon, oral rehydration solutions are more advisable for thirst than water because the osmotic gradient in the jejunal/ileal lumen will then be lower and the efflux of water and electrolytes less pronounced. Several reports indicated a beneficial effect of adding soluble fibre (pectin) which may serve as an additional source of energy, promoting more efficient electrolyte absorption, provided that the colon is in continuity (19, 22). Addition of glutamine is controversial (11, 28), but one recent study describes a beneficial effect from fish oil added to the enteral diet, on the reversal of cholestasis (29).

3. Parenteral Nutrition

3.1 Basic concepts

IF by definition precludes the ability of the residual functional bowel to absorb sufficient amount of nutrients, energy and water to sustain life and growth on oral/enteral intake. Therefore, for patients with IF parenteral nutrition is a life-saving procedure which has to be initiated in each patient after the initial water and electrolyte imbalances have been corrected. The ability to provide nutrition parenterally, sufficient to maintain health and growth in children with IF for long periods and in some cases for life, represents one of the most important developments of the 20th century. As long-term PN can be anticipated in a significant proportion of children with IF, the most important feature of PN management is to avoid the complications such as central catheter associated sepsis, loss of venous access, development of intestinal failure associated liver disease (IFALD) and inappropriate growth. How to do this with respect to the composition of the PN solution and prevention of the complications of central venous access will be described here, while IFALD will be discussed in a separate section below. For other details on how to provide PN to paediatric patients, readers are referred to the comprehensive, very recently revised ESPGHAN/ESPEN guidelines on parenteral nutrition in children (30) and to the LLL module number 10.2.

3.2 Composition of the PN Solution

Infants and children should receive *amino acid solutions* that are adjusted to their age, particularly with respect to the increased requirements for the amino acids considered semi-essential, such as arginine, cysteine, glycine, proline and tyrosine. While an amino acid supply should be initiated at the recommended dose from the initiation of PN, excess of nitrogen intake as well as any excess of energy should be avoided.
Glucose is the only carbohydrate to be used in paediatric PN, and it should normally provide 70% - 75% of the non-protein calories. The desired dose per kilogram of body weight is usually achieved by stepwise increases over several days aiming to avoid hyper- and hypoglycaemia. For the same reason, once cyclical PN is established, the rate of infusion is gradually increased and decreased over the initial and last 2-3 hours respectively. Excess energy provided as glucose may induce lipogenesis, liver steatosis, impaired protein metabolism, and enhanced CO_2 production (30).

The role of *lipid emulsions* is to provide essential fatty acids and some 25% to 30% of non-protein energy. Although it is still widely practiced to increase the rate of lipid infusion stepwise over several days, studies have not confirmed that this method improves lipid tolerance. Parenteral lipids have been implicated in the pathogenesis of IFALD for many decades with respect to the total dose and also to some constituents of the lipid emulsion. This appears particularly related to high ratios of omega-6 to omega-3 PUFAs, high intake of phytosterols, and a low concentration of the antioxidant alfa-tocopherol. Therefore, parenteral lipids have emerged as one of the most exciting areas of clinical research relevant to the prevention and treatment of IFALD, particularly in respect of the recent introduction of fish oil, either as the sole source of lipids or within mixtures consisting of soybean oil, coconut oil, olive oil and fish oil (reviewed in 3, 11, 15, 19, 31). A recent systematic review and position paper by the ESPGHAN Committee on Nutrition stated that, while in the short term no significant differences in outcomes are found, the addition of fish oil to the composite intravenous lipid emulsion may be beneficial for children on long term parenteral nutrition (32). According to the new ESPGHAN PN guidelines pure fish oil cannot satisfy essential fatty acid requirements and its use is therefore not recommended. It can only serve as a short term rescue treatment for patients with progression to severe IFALD. For children in whom long-term PN is expected, it appears prudent to use a composite intravenous lipid emulsion containing fish oil (30).

3.3 Compounding and Mode of Infusion

Patients with IF, particularly in the paediatric age group, do not have fixed nutritional requirements; on the contrary, requirements for water, energy and specific nutrients change with the adaptation of the residual bowel and also along with the growth and maturation of the child. Therefore, an individualized PN prescription tailored to the requirements of the individual patient has traditionally been preferred, particularly for long-term home PN. However, as for the stable hospitalized patients, standard ready-made PN mixtures could be a valuable option. Individualized PN admixtures can be used only if prepared in a sterile environment following good clinical practice guidelines (30).
Once the child with IF is stable on PN, with the enteral intake covering at least 30% of the nutritional requirements, cyclic PN provided over less than 24 hours (usually 10-14 hours) can be initiated. The cyclical mode is almost a prerequisite for home parenteral nutrition, and is associated with a reduced risk of liver complications, and with improved quality of life (33).

3.4 Venous Access

Establishing reliable venous access is a "*conditio sine qua non*" for patients with IF on PN (34). If prolonged PN will be required, a central venous catheter (CVC) made of silicon or polyurethane, tunnelled subcutaneously, and with a single lumen is recommended. If a multilumen CVC is used, one port should be exclusively designated for PN. Moreover, blood administration and central venous pressure monitoring from the designated port should be avoided. With respect to the insertion site, the subclavian vein is traditionally considered as the best approach. However, in infants and children femoral catheters are not associated with the higher incidence of mechanical complications seen in adults. As CVC insertion and usage could be associated with severe complications such as thrombosis and sepsis, a

multidisciplinary team approach with personnel proficient in paediatric PN is highly recommended (all extensively reviewed in ref 30). The importance of providing an aseptic approach during catheter insertion and its subsequent care cannot be overemphasized. In the past decade a number of studies have been performed aiming to reduce CVC-related blood stream infections providing data for the recently published evidence based guidelines (35, 36). Most recently, ethanol and taurolidine locks have been recommended as effective means to prevent CVC-related infection (30, 37, 38). However, the ethanol lock may also have a negative effect on catheter integrity and increase the rate of thrombotic occlusions (37, 39). As the rate of complications is much lower if the patient is at home, this is one among many other reasons to initiate home parenteral nutrition.

3.5 Home Parenteral Nutrition

Children with IF will, by definition, require PN for a prolonged period of time. For these patients, home PN (HPN) is the best option, providing clear benefits such as improved quality of life, 50% to 60% lower costs, and a significantly lower rate of infective CVC-related complications. However, several conditions should be fulfilled before initiating HPN: a. a stable clinical condition of the patient; b. enteral intake preferably exceeding 30% of nutritional requirements; c. establishment of cyclical PN; d. availability of a dedicated multidisciplinary nutrition care team 24 hours a day 7 days per week (30).

4. IFALD, Table 5

Intestinal failure associated liver disease – IFALD - is defined as hepatobiliary dysfunction developing as a consequence of medical and surgical management strategies for intestinal failure, which can variably progress to end-stage liver disease, or can be stabilized or reversed with promotion of intestinal adaptation (19, 40). It is the most prevalent potentially lethal complication affecting children with IF. Although there are many contributing factors, lack of EN and being exposed to long-term PN are the two most important. Factors associated with the liver injury and development of IFALD are listed in **Table 5**, while potentially protective factors and medical interventions include (19, 41):

1. Prevention of CVC related bloodstream infections with respect to:
    - strict adherence to an aseptic approach during CVC placement and subsequent care;
    - an aseptic compounding procedure;
    - home parenteral nutrition;
    - CVC locks with antibiotics, ethanol, taurolidine, heparin.
2. Early introduction of EN and subsequent use of oral/enteral feeds to the maximal concentration and volume that is tolerated without worsening the clinical symptoms
3. Prevention of bowel stasis / bacterial overgrowth either by applying oral antibiotics (metronidazole, trimethoprim, gentamicin, rifaximin, etc.) or by surgical procedures such as tapering in patients with distended immobile residual bowel segments.
4. With respect to the PN itself:
    - balanced energy supply + appropriate amounts of micronutrients and vitamins;
    - amino acid solutions adapted to the age of the child;

- a composite intravenous lipid emulsion with fish oil as one of the components could be beneficial, particularly for children on long-term PN, while a pure 10% fish oil can serve as a short-term rescue treatment for patients progressing to severe IFALD (30);
- cyclic PN.

Table 5
Factors associated with development of IFALD (19, 41, 53)

- **Factors associated with prematurity**
  - liver immaturity
  - early septic episodes
  - necrotising enterocolitis (NEC)
- **Factors associated with residual short bowel**
  - dilated residual bowel
  - intestinal stenosis / obstruction
  - impaired intestinal motility
  - blind loop syndrome / intestinal stasis
  - small bowel bacterial overgrowth / endotoxaemia
  - empty gut – lack of enteral feeding
  - impaired bile acid recirculation
- **Factors associated with PN composition**
  - amino acids not adjusted for the child's age
  - lipid emulsions with high phytosterol, low omega-3 PUFAs, and low alfa-tocopherol
  - high energy intake (high glucose and/or lipids)
- **CVC-related bloodstream infections**

5. Surgery

5.1 Reconstructive Surgery for Children with IF due to SBS

In the past several decades various surgical procedures have been developed to treat the problems that arise from IF due to SBS. Techniques are mainly focused on: a. insufficient length of the residual bowel (lengthening procedures); b. inefficient propulsive motility in dilated residual intestine (tapering and plication procedures to improve transit), and c. rapid intestinal transit - trying to slow it down (anti-peristaltic segments, artificial valves, colon interposition, recycling loops, etc.). Most important among them are the lengthening procedures, namely the intestinal lengthening and tailoring known as Bianchi procedure (42) and serial transverse enteroplasty (STEP) (43), which are relatively widely used and thoroughly discussed in several recent reviews (10, 44, 45). Briefly, the Bianchi lengthening technique can be applied if the residual bowel is significantly dilated and at least 30-40 cm in length. This dilated segment is divided into two hemi-loops which are re-anastomosed in an isoperistaltic manner. In STEP dilated bowel is cut perpendicularly to the long axis of the bowel, in a zigzag pattern from alternating sides restoring integrity by stapling so as to increase length and reduce diameter. Both techniques achieve similar survival (80%-90%) with a comparable percentage of patients who can be completely weaned from PN (50% - 55%) (17). In the same time they correct / tapper the dilated intestine, correct dysmotility, and improve intestinal absorption, decreasing the need for intestinal transplantation. The best timing is after the intestinal adaptation has achieved its maximal extent, but before

development of complications (bowel stasis). Detailed descriptions are beyond the scope of this text and readers are referred to other literature (42-45).

5.2 Intestinal Transplantation

Intestinal transplantation is a last resort, reserved for patients with SBS who do not achieve enteral autonomy and at the same time develop life-threatening complications such as end-stage IFALD, loss of venous access, or recurrent severe septic episodes, and who are therefore often referred to as "patients with nutritional failure" (11). Candidates also include patients with other causes of IF, particularly children with severe congenital enteropathies. Previously, there were expert opinions suggesting that intestinal transplantation should be used more frequently as a second option equivalent to life-long PN in permanent IF patients. However, the 5- to 10- years survival prognosis is clearly better for home PN (90%-70%) than for intestinal transplantation (75%-43%), particularly if children with IF are treated in expert centres with established multidisciplinary intestinal rehabilitation programmes (46-48). The improved results of conservative treatments based on intestinal rehabilitation programmes are the likely cause for the recent significant decrease in the number of paediatric intestinal transplants (10, 48). Therefore, the current view is that intestinal transplantation is a life-saving procedure reserved for patients with permanent nutritional failure (10, 11, 46).

6. Role of Intestinal Rehabilitation Programmes & Novel Treatments

IF is an uncommon condition of complex pathophysiology with a wide array of potential complications associated with high morbidity and mortality, and exceptionally high healthcare costs. Patients require repetitive prolonged hospitalizations, multiple surgical procedures, different medical treatments and highly specialized nutrition support (49). To achieve all these requires expertise in different clinical fields such as gastroenterology, dietetics, surgery, pharmacy and pharmacology, psychology, high quality nursing, etc. Such a holistic multitasking approach is feasible only if it is carried out by an expert multidisciplinary team, and in an institution specially equipped for the centralized care of IF patients. Management of IF within intestinal rehabilitation programmes in specialized centres is the current state of the art showing clear benefits with respect to reduction in septic episodes, decreased incidence of IFALD, decreased costs, etc. (3, 14, 46, 49, 50). Moreover, centralized health care in institutions with well-developed multidisciplinary intestinal rehabilitation programmes has resulted in significantly improved outcome of IF, followed by a reduction in the requirement for intestinal transplantation (3, 14, 46, 48-50). Those centres are also the place to evaluate novel treatments aiming to increase enterocyte absorption and foster intestinal adaptation, an example of which is the GLP-2 analogue teduglutide. The native hormone is produced by the L-cells of the terminal ileum and colon in response to luminal nutrients and has a pro-adaptive effect with a net increase in their digestion and absorption. Patients with resected ileum and colon and subsequent low levels of the GLP-2 could be the best candidates. Results of studies are emerging, but in children are still insufficient for conclusions to be unequivocal (51, 52).

7. Summary

IF is a condition of severe intestinal malabsorption due to a reduction of the functional gut mass below the minimum needed to absorb nutrients and fluids required to maintain weight on oral intake in adults, and to sustain age-appropriate growth and development in children. It therefore requires parenteral nutrition for various periods of time – sometimes for life, and also from the beginning, enteral nutrition in a ratio adjusted to the residual absorptive and digestive capacities of each individual patient**.**

In this module the aetiology and pathophysiology of IF are discussed with the aim of providing a logical theoretical background for the various aspects of nutrition treatment required in paediatric patients with intestinal failure. There is special emphasis on the short bowel syndrome as it is by far the most common cause of IF in children. How to perform parenteral and enteral nutrition to support growth and development, but also to prevent or minimize the numerous potential complications is thoroughly elaborated. Finally, surgical intestinal reconstruction, transplantation surgery, and the role of multidisciplinary intestinal rehabilitation programmes are summarized.

8. References

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