

Intestinal failure in childhood

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Abstract

Intestinal failure (IF) requires the use of parenteral nutrition (PN) for as long as it persists and in case of irreversible IF may be an indication for intestinal transplantation (ITx). Biological evaluation of IF is becoming possible with the use of plasma citrulline as a marker of intestinal mass. Short bowel syndrome (SBS) is the leading cause of intestinal failure in infants while few epidemiological data are to date available. Data on morbidity and mortality in paediatric patients with SBS are very limited but long-term outcomes seem to be improving. Other causes of intestinal failure include neuro-muscular intestinal disease and congenital disease of enterocyte development. The management of IF should include therapies adapted to each type and stage of IF based on a multidisciplinary approach in centres involving paediatric surgery, paediatric gastroenterology, parenteral nutrition expertise, home-parenteral nutrition programme, liver-intestinal transplantation experience. Timing of referral of patients in specialised centres remains a crucial issue.

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Intestinal failure (IF) results from the critical reduction of functional gut mass below the minimal amount necessary for adequate digestion and absorption to satisfy body nutrient and fluid requirements for maintenance in adults or growth in children. IF requires parenteral nutrition (PN) for as long as it persists.

Short bowel syndrome (SBS) was one of the first recognised conditions of protracted IF. With the increasing and successful use of long-term PN during the last three decades, several other causes of IF have emerged.

Long-term PN and home-PN are the mainstay of therapy, independent of the nature of "Intestinal failure" (IF) which can be total or partial, permanent or temporary.¹⁻³ Some patients remain partially or almost fully dependent on PN for years or forever and are thus considered to have permanent IF. Complications of IF and/or PN limiting the use of long-term PN raise the question of intestinal transplantation (ITx).

Assessment of intestinal failure

Citrulline, a non essential amino acid, mostly produced by enterocytes is a biological marker of functional gut mass.^{4,5} Studies performed in children with short bowel syndrome also emphasise the value of plasma citrulline as a biomarker of gut mass.^{6,7} Whether plasma citrulline levels are predictive of intestinal recovery, or not, remains to be confirmed. One of the best indicators for predicting full recovery of intestinal function remains the growth of the child as reflected in normal weight gain and growth velocity for age when fully, orally and/or enterally, fed.

Causes of intestinal failure

Short bowel syndrome

The incidence of SBS is difficult to establish, ranging between 2 and 5 per million live births.⁸ The causes of SBS differ significantly between series (Table I).⁸⁻¹¹ Necrotising enterocolitis (NEC) remains the leading cause of SBS especially in premature infants. The percentage of SBS caused by NEC ranges from 14 to 43% depending on the country that data originate from.⁹⁻¹³ Several studies included in a meta-analysis have shown that probiotics administration might be helpful in decreasing incidence of NEC in preterm infants.¹⁴ Other causes of short bowel syndrome include resection following intestinal atresia, gastroschisis, other congenital malformation including midgut volvulus from malrotation, and radiation enteritis. Crohn's disease should no longer be a cause of SBS resulting from repeated small bowel resection.

Survival of SBS infants has increased during the last decades. More than 80 % of infants and children now survive after extensive small bowel resection in the neonatal period.^{9,15} Prognosis is related to age adjusted intestinal length, ileocaecal valve (ICV), colon preservation and occurrence of cholestasis. In SBS patients most of the deaths are caused by liver failure or sepsis and occur within one year post-event. A survey including 87 children who had undergone extensive neonatal SB resection, were followed up over a mean 15 year-period.⁹ The overall survival was 89.7% depending on the year of birth. By multivariate analysis, PN duration was significantly influenced by the length of residual intestine and the absence of ileocaecal valve. After PN weaning, they grow up normally with normal puberty and final height as expected from genetic target height.

Nutritional support: In order to maintain an optimal nutritional status with normal growth and development oral feeding skills have to be acquired and maintained. PN is the corner stone of management but as much nutrition as possible should be provided to the patient via the enteral route in order to improve the physiological processes of intestinal adaptation. Oral feeding, which is known to enhance GI secretions, salivary Epidermal Growth Factor (EGF) release and gallbladder motility, is recommended. In addition, oral feeding by promoting gut motility improves intestinal bacterial clearance thus reducing the risk of small intestinal bacterial overgrowth.¹⁶ However the mode of administration of feeding varies among different practitioners regarding the composition of the enteral feed (elemental, semi-elemental or polymeric) and mode of delivery (gastric tube feeding or oral feeding).¹⁷ Moreover current studies do not provide evidence based recommendations for using special diets such as amino acid based enteral formulae. Long term follow up of growth after PN weaning is mandatory in order to decide on the need to restart nutritional support, when required.⁹

Rehabilitation therapies for short bowel patients

Intestinal flora related disorders

The colon is a crucial partner for small intestinal adaptation and function in patients who underwent extensive small intestinal resection.¹⁸

However, colonic hypermetabolism may be responsible for D-lactic acidosis resulting from fermentation of dietary carbohydrate by luminal bacteria in the small bowel. D-lactic acidosis may be associated with clinical symptoms and failure to thrive.¹⁹

Small bowel bacterial overgrowth (SBBO) is a frequent complication that is likely to occur in the case of ICV resection, poor motility of a dilated small bowel segment, or when a tight anastomosis is present. SBBO is mostly responsible for mucosal inflammation, which may further exacerbate nutrient malabsorption and protein sensitisation, deconjugate bile salts and deplete bile salt pool with subsequent impaired micellar solubilisation resulting in steatorrhea and fat soluble vitamins malabsorption. SBBO increases the risk of intestinal bacterial translocation which increases the risk for liver disease.^{20,21}

Antibiotic therapy should be used very cautiously and with due attention to their effects on the colonic bacterial microflora which should be preserved for production of short chain fatty acids. The use of probiotics might be helpful but it is not yet been adequately documented in SBS paediatric patients.²²

Non-transplant surgery: Surgical procedures have been proposed for increasing nutrient and fluid absorption by either slowing the transit or increasing surface area. Such procedures include intestinal valves, reversed intestinal segments, colon interposition, but have all yielded conflicting results.²³

In selected patients with dilated bowel segments, longitudinal intestinal lengthening and tailoring (LILT) have been extensively performed.²⁴ LILT has the theoretical benefit of not only tapering the dilated segment but also of using the divided intestine to increase total small bowel length. The anatomical criteria that have been suggested for patient selection for this procedure include (i) intestinal diameter (> 3 cm); (ii) length of residual small bowel (> 40 cm);

and (iii) length of dilated bowel (> 20 cm). This procedure allows improvement in more than 50% of patients in terms of intestinal transit time, stool frequency, intestinal absorption rate, weight gain and PN weaning.²⁵ LILT is not yet recommended for patients with severe liver disease or cirrhosis.

Serial transverse enteroplasty (STEP) has also been reported for use in infants and children with SBS.²⁶ Indications for the procedure have broadened STEP's use beyond the scope of SBS to include bacterial overgrowth and neonatal intestinal obstruction with dilated proximal intestine. The first 38 patients enrolled in the International STEP Data Registry were reviewed.²⁷ More data are required to establish the long term safety and efficacy of the procedure, with the goal of improving patient selection criteria and optimal time of surgical intervention.

Trophic factors

The use of recombinant human growth hormone (rhGH) is associated with conflicting results in adult patients with SBS who were included in both, open and/or randomised clinical trials.^{28,29} Few such studies have been reported in children with SBS.^{30,31}

Glucagon-like peptide-2 (GLP-2) has been reported to improve intestinal absorption and nutritional status in SBS patients with impaired postprandial GLP-2 secretion in whom the terminal ileum and the colon had been resected.³² The results of a paediatric study suggest that in infants with intestinal dysfunction, GLP-2 levels are correlated with residual small bowel length and nutrient absorption, and may be predictive of outcome.³³ GLP-2 might be the most logical medical approach for early management of SBS patients especially those with ileal resection. To date, there are no published studies involving infants or children.

Epidermal growth factor (EGF) has also been shown to have a role both in maintaining epithelial tissues as well as controlling intestinal adaptation.³⁴ Five SBS paediatric patients (< 25% bowel length predicted for age) were treated with human recombinant EGF.³⁵ However, this study does not allow drawing any conclusion.

Insulin influences intestinal structure and absorptive function.³⁶ The favourable effect of insulin is relevant and might be considered in patients on PN receiving high intravenous glucose rate that induce insulin release and relative hyperinsulinism. Interestingly, oral insulin has been shown to enhance intestinal adaptation following massive resection in a rat model.³⁷

Intestinal neuromuscular diseases

Total colonic aganglionosis (TIA) with jejunio-ileal involvement

This condition is a rare form of Hirschsprung disease (HD). The aganglionosis may extend to encompass the entire colon (total colonic aganglionosis) or very rarely affect the entire intestine (TIA). When the normal ganglionic small bowel is shorter than 50 cm, the probability for permanent PN dependency is high. There is no surgical procedure that can improve intestinal absorption without the colon. Thus, TIA with jejunio-ileal involvement is equivalent to short bowel syndrome without colon. Small bowel transplantation is the ultimate cure. Several patients with a length of normal bowel segment ranging from 15 to 50 cm have been transplanted.³⁸

Chronic intestinal pseudo-obstruction syndrome (CIPOS)

This is a very heterogeneous condition in terms of clinical presentation, histopathological features, severity of motility disorders and outcome.³⁹ Patients with the most severe form of CIPOS, whether myopathic or neuropathic with or without urinary tract involvement, are very uncomfortable because of the association of enterostoma, gastrostomy tube, central line and sometimes vesicostomy. ITx becomes logical, but difficult, because of the requirement of multiple previous surgical procedures and associated disorders such as uropathy or peripheral neuropathy.⁴⁰

Congenital enteropathy

Microvillous atrophy (MVA)

Among the causes of intractable diarrhoea of early infancy,⁴¹ MVA is a congenital constitutive intestinal epithelial cell disorder leading, in its typical early-onset form, to PIF. MVA is characterised by a lack of microvilli on the surface of enterocytes and the occurrence of intracellular vacuolar structures containing microvilli, Microvillous Inclusion Disease (MVID).⁴² Following homozygosity mapping in a single kindred with MVID, nonsense and missense mutations in MYO5B, encoding type Vb myosin motor protein were identified. In addition, mislocalisation of transferrin receptor in MVID enterocytes suggests that MYO5B deficiency causes defective trafficking of apical and basolateral proteins in MVID.⁴³

The largest multi-centre survey of 23 MVA patients⁴⁴ revealed an extremely reduced life expectancy with a one-year survival rate of less than 25%. Most children died of septic complications, liver failure or metabolic decompensation. Management is based on PN since all other medical approaches have failed. Complications related to inadequate PN do limit long-term survival. Finally, even with adequate long-term PN and normal growth, most children continue to manifest high and disabling levels of stool output that results in a high risk for severe dehydration and requires daily fluid and electrolyte replacement. Thus, ITx has become the only definitive treatment for this rare intestinal disease. ITx usually involves isolated intestine or intestine combined with the liver and colon.⁴⁵

Intestinal epithelial dysplasia (IED) or tufting enteropathy

Congenital tufting enteropathy (CTE) is a rare autosomal recessive diarrhoeal disorder presenting in the neonatal period. CTE is characterised by intestinal epithelial cell dysplasia leading to severe malabsorption and significant morbidity and mortality.^{46,47} The pathogenesis and genetics of this disorder are not well understood. Mutations in the gene for EpCAM are responsible for CTE.⁴⁸ Several cases of CTE have been reported as being associated with phenotypic abnormalities such as choanal atresia, rectal atresia, esophageal atresia and a non-specific punctiform keratitis involving about 60% of patients.

This cause of neonatal diarrhoea requires permanent PN. However, it would appear that some infants have a rather milder phenotype than others. Because of the preservation of some degree of intestinal function and a more limited volume of stool output, some patients need only partial long-term PN. Even in such cases, careful monitoring should be implemented in order to avoid progressive growth retardation. In most patients, the severity of intestinal malabsorption and diarrhoea, however, make such patients totally

dependent on long-term PN with its attendant complications. In such patients intestinal transplantation may, thus, become an indication.

Autoimmune enteropathy (AIE) causes severe IF.⁴⁹ Mutations in the *FOXP3* gene cause AIE.⁵⁰ Non-functional *FOXP3* leads to a tremendous hyperactivation of T cells, resulting in autoimmune aggression, such as seen in patients with immune dysregulation, polyendocrinopathy autoimmune enteropathy X-linked (IPEX) syndrome, a subgroup of AIE. The use of T-cell immunosuppressive drugs, such as tacrolimus or rapamycin following steroids treatment, seems to be beneficial in some patients. However, long-term remission is not always possible.⁵¹ Bone marrow transplantation might be the treatment of choice in those patients who do not respond to immunosuppression.^{52,53}

From intestinal failure to intestinal transplantation

PN and home-PN remain the mainstay of therapy, independent of the nature of IF which can be total or partial, permanent or temporary.^{2,3,54} However, some patients develop complications while receiving daily long-term PN for IF. These patients can be considered as candidates for intestinal transplantation.

Intestinal failure-related liver disease

Cholestasis and liver fibrosis are associated with impaired intestinal function, disruption of enterohepatic cycle (ileal disease or resection), intestinal stasis with subsequent intra-luminal bacterial overgrowth and/or translocation (endotoxemia), recurrent catheter related sepsis, while prematurity itself might be an associated factor aggravated by inadequate PN.³ Preventing or reversing liver disease is possible by stimulating the enterobiliary axis by early oral/enteral feeding, by reducing intra-luminal bacterial overgrowth, by using ursodesoxycholic acid, by preventing catheter related sepsis, and by providing adapted PN with appropriate amino acids solutions, lipid emulsions, micronutrients provision and cyclic infusion.³ The guidelines on PN provide extensive recommendations for adapting nutritional support.⁵⁴

Some SBS children with a length of remnant intestine theoretically sufficient to achieve PN weaning, liver disease interferes with gut adaptation and can lead to early death. The small size and poor condition of these infants means they are poor candidates for combined liver-intestine Tx, while many of them die before a combined graft is available. Case reports or small samples of isolated liver transplantation (ILTx) in SBS paediatric patients have been reported.⁵⁵ Prevention of NEC, screening for high risk patients such as gastroschisis or NEC and prevention of IF related liver disease might improve outcome for such patients and decrease the need for any type of liver grafting alone or in combination with small intestine.^{3,56}

Indications for Intestinal Transplantation

Some patients may remain partially or almost fully dependent on PN for years or forever and are thus considered to have permanent IF. Moreover, patients who develop complications while receiving daily long-term PN for IF are candidate for ITx. A European survey⁵⁷ studied the candidacy of home-PN patients for ITx and timing for referral for ITx. Candidacy was assessed by the USA Medicare and American Transplantation Society criteria,^{58,59} categorised as:

- (i) life-threatening home parenteral nutrition (HPN) complications;
- (ii) high risk of death due to the gastrointestinal disease; and
- (iii) IF with high morbidity or patient HPN refusal.

On the basis of these criteria, physicians judged candidacy for ITx as immediate or potential. The main indications for HPN were SBS (52%), chronic intestinal pseudoobstruction syndrome (CIPOS) (25%) and congenital mucosal disease (14.5%). Candidacy was considered for 57 patients (34.3%) with the following underlying disease: congenital enteropathy (26.3%), CIPOS (26.3%), SBS (19.3%). Immediate candidacy was judged for 15.8% of paediatric candidates (i.e. < 50% of candidates because of HPN-related liver failure).

The irreversibility of SBS related IF has to be demonstrated before any ITx can be considered. IF may be clearly and early considered as *irreversible* in patients with duodenocolic anastomosis after extensive intestinal resection for midgut volvulus or children with total aganglionosis with small bowel length less than 50 cm and infants suffering congenital enteropathy such as MVID or IED. All these patients are potential candidates for ITx. Since these patients will remain indefinitely dependent on PN, they must be referred early for transplantation on good nutritional status and with the minimal possible IF and PN related complications. Severe liver disease should no longer be considered as an indication for ITx. In contrast, it can be rather difficult to confirm irreversibility of IF in SBS or CIPOS patients for which all medical and/or surgical approaches have to be tried before any decision of ITx can be taken.³ In these particular cases, if long-term PN is effective and well-tolerated, it can be used for a prolonged period of time without ITx. Finally, few patients require immediate transplantation for life threatening conditions.⁵⁷

Extensive multidisciplinary discussion involving transplant surgeons, paediatric gastroenterologists, specialised nurses, dieticians, social workers and psychologists is mandatory before any decision is taken for a specific child. Assessment and decisions should be based on the occurrence of the complications listed in the position paper of the American Society of Transplantation.⁶⁰

Type of intestinal transplantation

Children with severe advanced and progressive hepatic fibrosis are usually listed for LITx. However, some PN-dependent patients with advanced liver dysfunction may experience functional and biochemical liver recovery which appears to parallel autologous gut salvage.^{61,62}

Factors impacting adversely on the survival of children with intestinal failure referred for ITx include : age below one year, multiple prior surgery, bridging fibrosis or cirrhosis, bilirubin levels over 3 mg/dl, and thrombocytopaenia.⁶³ The United Network for Organ Sharing (UNOS) report indicates that mortality on the ITx waiting list is higher than on any other transplant waiting list.⁶⁴ The ITx Registry confirmed that transplantations performed in patients waiting at home *versus* waiting in hospital have a better than one-year survival (74% versus 59%; $P < 0.00001$).⁶⁵ The trend to transplant proportionately more patients who are waiting at home was a major factor contributing to the recently improved graft and patient survival rates.⁶⁵ Indeed, it is well established that patients with end stage liver disease are at risk of dying before transplantation and are also at higher risk of post-operative complications and death.^{63,64} We recently reported factors impacting on survival after Tx.⁶⁶ Such factors should also be considered before listing a patient for ITx.

Intestinal failure rehabilitation centre

Long-term management of IF has become a very important goal. Few centres manage all the stages of IF from onset to ITx, including home PN programmes.^{2,67} SBS remains the most common indication for ITx accounting for 63% of case *versus* 32% of other indications in our transplantation centre.^{65,66} Liver complications of poor functioning remnant small intestine with intestinal stasis and subsequent sepsis from bacterial overgrowth may be prevented by appropriate medico-surgical approaches. In addition to the prevention of complications, global management should also aim to demonstrate the irreversibility of IF in spite of all medico-surgical attempts at digestive autonomy.³

The development of integrated centres involved in all stage of IF management should be encouraged. Such centres should have a high level of expertise in the fields of paediatric Gastroenterology and Clinical Nutrition with a well organised Home-PN programme, together with experienced paediatric surgeons involved in SBS-non-transplant surgery as well as in intestinal transplantation.^{67,68} ITx offers not only an improved quality of life but also maintains optimal nutritional status.^{69,70}

Table I: Main causes of short bowel syndrome

	International ⁸	France ⁹	Canada ¹⁰	USA ¹¹
Intestinal atresia	23%	39%	30%	30%
Volvulus	24%	24%	10%	10%
Gastroschisis	14%	14%	12.5%	17%
NEC	27%	14%	35%	43%

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