DEFINITION

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) as long as it persists.

Long-term PN and home-PN are the mainstay of therapy, independent of the nature of “intestinal failure” 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 limiting the use of long-term PN raise the question of intestinal transplantation (ITx).

ASSESSMENT OF INTESTINAL FAILURE

Citrulline has been recently proposed as a biological marker of intestinal mass. It is a non-essential amino acid, mostly produced by enterocytes. Plasma citrulline levels reflect the loss of functional mass in patients with various degree of villous atrophy or during intestinal graft rejection with subsequent villous atrophy(4,5). Studies performed in children with short bowel syndrome also emphasize the value of plasma citrulline(6,7). Citrulline might be a
marker for the gut-trophic effects of bowel rehabilitation therapies. Whether plasma citrulline levels are predictive of intestinal recovery, or not, has to be confirmed. However, the best indicator for predicting full recovery of intestinal function remains the growth of the child, as reflected in normal weight gain and growth velocity for age while fully enterally fed.

**CAUSES OF INTESTINAL FAILURE**

Short bowel syndrome (SBS) was one of the first recognized 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 such as chronic intestinal pseudo-obstruction syndrome or more recently, congenital diseases of enterocyte development.

**A. Short Bowel Syndrome**

*Cause and epidemiology*

Incidence of SBS is difficult to establish, ranging between 2 and 5 per million live births(8). The causes of SBS differ significantly between studies (Table 1)(8-11). Necrotizing enterocolitis (NEC) remains the leading cause of SBS especially in premature infants. The percentage of SBS caused by NEC range from 14 to 43%(9-12). Several studies and a meta-analysis have shown that probiotics administration might be helpful in decreasing incidence of NEC in preterm infants(13-15). Other causes of short bowel syndrome include resection following intestinal atresia, gastroschisis, other congenital malformation including midgut volvulus from malrotation, and radiation enteritis. Crohn disease should no longer be a cause of SBS resulting from repeated small bowel resection.

**Management and outcome**

Survival has increased during the last decades. More than 80 % of infants and children now survive after extensive small bowel resection in the neonatal period (9,16,17). Prognosis is related to age adjusted intestinal length, ileocecal 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 1 year. A survey including 87 children who undergone extensive neonatal SB resection, followed up them over a mean 15 years- period (9). The overall survival was 89.7% depending on the year of birth. By multivariate analysis, PN duration is significantly influenced by the length of residual intestine and the absence of ICV. After PN weaning, they grow up normally with normal puberty and final height as expected from genetic target height.

**Nutritional support:** Maintain an optimal nutritional status with normal growth and development. Oral feeding skills have to be acquired or maintained. PN is the cornerstone of management, but as much nutrition as possible should be provided to the patient via the intestine in order to improve the physiological processes of intestinal adaptation. Oral feeding enhances GI secretions, salivary EGF release and gallbladder motility, and is recommended. However, the mode of administration of feeding varies among different groups regarding the optimal composition (elemental, semi-elemental or polymeric) and mode of delivery (gastric tube feeding or oral feeding) of diet(18). Moreover, current studies do not provide evidence based recommendations for using special diets such as amino acid based formulas.

**Rehabilitation therapies**

*Intestinal flora related disorders:* The colon becomes an important digestive organ while it markedly influences the delay of adaptation(19). 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(20).

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**TABLE I MAIN CAUSES OF SHORT BOWEL SYNDROME**

<table>
<thead>
<tr>
<th>Condition</th>
<th>International (8)</th>
<th>France (9)</th>
<th>Canada (10)</th>
<th>USA (11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestinal atresia</td>
<td>23%</td>
<td>39%</td>
<td>30%</td>
<td>30%</td>
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<tr>
<td>Volvulus</td>
<td>24%</td>
<td>24%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Gastroscisis</td>
<td>14%</td>
<td>14%</td>
<td>12.5%</td>
<td>17%</td>
</tr>
<tr>
<td>Necrotising enterocolitis</td>
<td>27%</td>
<td>14%</td>
<td>35%</td>
<td>43%</td>
</tr>
</tbody>
</table>
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, 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 and increases hepatotoxicity related to PN(21,22).

Antibiotic therapy should be very cautious according to its effects on the colonic bacterial microflora, that should be preserved for production of SCFA. The use of probiotics might be helpful but is not yet validated in SBS pediatric patients(23).

Non-transplant surgery: Surgical procedures have been proposed in unadapted SBS for increasing nutrient and fluid absorption by either slowing the transit or increasing surface area. These include: intestinal valves, reversed intestinal segments, colon interposition, all providing conflicting results(24).

In selected patients with dilated bowel segments, longitudinal intestinal lengthening and tailoring (LILT) has been extensively performed(25). LILT has the theoretical interest of not only tapering the dilated segment but also of using the divided intestine to increase total small bowel length. Anatomical criteria have been suggested for patient selection for this procedure: (i) intestinal diameter >3cm; (ii) length of residual small bowel >40cm; (iii) length of dilated bowel >20cm. This procedure allows improvement in more than 50% of patients in terms of intestinal transit, stool frequency, intestinal absorption rate, weight gain and finally PN weaning(26). It is yet not recommended to perform the LILT procedure in patients with severe liver disease or cirrhosis. A new procedure called serial transverse enteroplasty (STEP) was reported for infants and children with SBS(27). STEP is a simple bowel-lengthening procedure with promising early surgical and nutritional outcomes. The first 38 patients enrolled in the International STEP Data Registry were reviewed(28). Median followup from STEP procedure to analysis was 12.6 months (range 0 to 66.9 months). Mean small intestine length was substantially increased in all groups (68+44 cm versus 115+87 cm, P<0.0001, n=27). Notable complications included intraoperative staple line leak (n=2), bowel obstruction (n=2), and fluid collection or abscess (n=3). Late outcomes included progression to transplantation (n=3) and mortality (n=3). For the short bowel syndrome cohort, enteral tolerance was notably increased from 31%+31% to 67%+37% of calories (P<0.01, n=21). Indications for the procedure have broadened beyond the scope of SBS to include bacterial overgrowth and neonatal intestinal obstruction with dilated proximal intestine. More data is required to establish the long term safety and efficacy of the procedure, with the goal of improved patient selection and operative timing.

Trophic Factors

Recombinant human growth hormone (rhGH) provided conflicting results in adult patients with SBS involved in both open and randomized clinical trials(29,30). Few studies have been currently reported in children with SBS(30,31). Results suggested beneficial effect of rhGH by decreasing the need for PN with only mild effects on body composition and gut mucosa. In addition there was no apparent benefit from glutamine treatment.

Glucagon-like peptide-2 (GLP-2), a 33 amino acid peptide-encoded carboxyterminal to the sequence of GLP-1 in the proglucagon gene is produced by L cells in the ileum in response to luminal nutrients. GLP-2 improves intestinal absorption and nutritional status in SBS patients with impaired postprandial GLP-2 secretion in whom the terminal ileum and the colon have been resected, based on the hypothesis that distal small bowel and caecal resection would decrease GLP-2 levels and reduce adaptation(33). The results of a pediatric 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(34). GLP-2 might be the most logical medical approach for early
management of SBS patients especially those with ileal resection. To date, there is no published study involving infants or children.

Epidermal growth factor (EGF) has been shown to have a role both in maintaining epithelial tissues as well as controlling intestinal adaptation(35). Five SBS pediatric patients (<25% bowel length predicted for age) were treated with human recombinant EGF(36). However, this study does not allow drawing any conclusion.

Insulin influences intestinal structure and absorptive function(37). 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 was shown to enhance intestinal adaptation following massive resection in a rat model(38).

B. Intestinal Neuromuscular Diseases

Total colonic aganglionosis with jejuno-ileal involvement.

It is a rare form of Hirschsprung disease (HD). In 80% of infants, the aganglionosis is confined to the rectum and sigmoid, but it may extend to encompass the entire colon (total colonic aganglionosis) or very rarely affect the entire intestine. When the normal ganglionic small bowel is shorter than 50cm, the probability for permanent PN dependency is high. There is no surgical procedure such as reverse loops, Kimura procedure or longitudinal myomectomy improving the intestinal absorption. Total colonic aganglionosis with jejuno-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(39).

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(40,41). Patients with the most severe form of CIPOS, whatever 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. Intestinal transplantation becomes logical, but is difficult because of requirement of multiple previous surgical procedures and associated disorders such as uropathy or peripheral neuropathy(42,43).

C. Congenital Enteropathy

Congenital diseases of enterocyte development such as microvillus atrophy (MVA) and intestinal epithelial dysplasia (IED) cause intestinal failure. Onset of either disorder is within the first few days or weeks of life in form of severe watery diarrhea. MVA involves the intracellular pathway of brush border development and the assembly of the plasma membrane of enterocytes(44). In contrast, IED is associated with an abnormal basement membrane structure as suggested by an abnormal deposit of laminin as well as a2b4 integrin and desmoglein expression(45,46). For both disorders, the primary defect is currently not known and genetic studies are underway. Most patients suffering from a constitutive disorder of intestinal epithelial cells remain permanently dependent on PN and are logical candidates for intestinal transplantation. Small bowel transplantation was reported for MVA patients in variable association with liver and/or colon(47,48). Patients with IED successfully underwent either an isolated intestinal transplantation or in combination with the liver in case of end stage liver disease(49,50). The largest survey was recently reported with 86% one year survival after intestinal transplantation(51).

Autoimmune enteropathy (AIE) causes severe IF(52). Mutations in the FOXP3 gene cause AIE(53). 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 rapamycine following steroids treatment, seems to be beneficial in some patients, however, long term remission is not always possible(54). Bone marrow
transplantation might be the treatment of choice in those patients who do not respond to immunosuppression(55). Conversely, intestinal transplantation is not indicated yet for autoimmune enteropathy or IPEX. A new mutation within an upstream noncoding region of FOXP3 results in a variant of IPEX syndrome associating autoimmune and severe immunoallergic symptoms(56).

**FROM INTESTINAL FAILURE TO INTESTINAL TRANSPLANTATION**

PN and home-PN remains the mainstay of therapy, independent of the nature of IF which can be total or partial, permanent or temporary(2,3,57). In addition, some patients develop complications while receiving daily long-term PN for IF. These patients can be considered as candidates for intestinal transplantation(ITx). Some patients may remain partially or almost fully dependent on PN for years or forever and are thus considered to have permanent IF. The number of patients with IF is certainly much smaller than the number of those suffering from renal failure, or end stage liver disease. However very few data are available to estimate the human and economic impact of IF in the pediatric population. Patient’s status and referral for intestinal transplantation remain debated. Intestinal Transplant Registry as well as report from individual programs demonstrated the relationship between patient’s pre-Tx status and outcome. On the other hand, candidacy for ITx was analysed in a European survey of home-PN patients. Early referral and listing are important for successful outcomes after intestinal grafting.

**INTESTINAL FAILURE RELATED LIVER DISEASE**

Cholestasis and liver fibrosis are related to the impaired intestinal function : disruption of enterohepatic cycle (ileal disease or resection), intestinal stasis with subsequent intra-luminal bacterial overgrowth and/or translocation (endotoxinemia); 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 enterohepatic axis by early oral/enteral feeding, by reducing intra-luminal bacterial overgrowth, by using ursodesoxycholic acid, by preventing catheter related sepsis, by providing adapted PN with appropriate amino acids solutions, lipid emulsions, micronutrients provision and cyclic infusion(3). The recently published guidelines on PN provide extensive recommendations for adapting nutritional support(57).

However, some infants, especially premature babies with severe NEC or term neonates with SBS from gastroschisis and/or extensive intestinal atresia, are at high risk of developing early end stage liver disease because of disruption of enterohepatic cycle and intestinal stasis, protracted bowel rest, continuous lipid free PN infusion, and repeated catheter related sepsis(58).

In 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 in SBS pediatric patients were reported(59,60). Prevention of NEC, screening for high risk patients such as gastroschisis and prevention of IF related liver disease might improve outcome for those patients and decrease the need for any type of liver grafting alone or in combination with small intestine(3).

**INDICATIONS FOR INTESTINAL TRANSPLANTATION**

Patients who develop complications while receiving daily long term PN for IF are candidate 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. A European survey(61) studied the candidacy of home PN patients for intestinal transplantation and timing for referral for ITx. Candidacy was assessed by USA Medicare and American Transplantation Society criteria(62,63), categorized 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.

Physicians judged candidacy 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 mucosal disease (26.3%), CIPOS (26.3%), SBS (19.3%); immediate candidacy was required for 15.8% of pediatric candidates (< 50% of candidates because of HPN-related liver failure).

The irreversibility of SBS related IF has to be demonstrated before any project of ITx. 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. Patient suffering congenital enteropathy such as MVID or IED have irreversible intestinal failure. 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 accumulation of IF and PN related complications. Severe liver disease should no longer be the 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 intestinal transplantation. Finally, as shown in the European study by Pironi, et al.(61), few patients require immediate transplantation for life threatening conditions.

Extensive multidisciplinary discussion involving transplant surgeons, pediatric gastroenterologists, specialized nurses, dieticians, social workers and psychologists is mandatory before any decision is taken for a specific child. Assessment and decision are based on the occurrence of the complications listed in a position paper of the American Society of Transplantation(64).

**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(65).

Factors impacting the survival of children with intestinal failure referred for ITx include: age below 1 year, multiple prior surgery, bridging fibrosis or cirrhosis, bilirubin levels over 3 mg/dl, and thrombocytopenia(66). The UNOS report indicates that mortality on intestine transplant waiting list is higher than on other transplant waiting lists(67). The Intestine Transplant Registry confirmed that transplantations performed in patients waiting at home versus waiting in hospital have a better one-year survival (74% versus 59%; P<0.00001)(68). 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(68). Indeed, it is well

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**Key Messages**

- Intestinal failure results from the critical reduction of functional gut mass below the minimal amount necessary for adequate digestion and absorption.
- Short bowel syndrome (SBS) is the most frequent cause of protracted intestinal failure.
- Parenteral nutrition remains the mainstay of therapy of intestinal failure.
- Intestinal failure patients are candidates for Intestinal transplantation.
- Development of integrated centers involved in all stage of management of intestinal failure should be encouraged.

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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(66,67). We recently reported factors impacting survival after Tx(69). Such factors should also be considered before listing for transplantation.

**Inestinal Failure Rehabilitation Center**

Long-term management of IF has become a very important concern. Few centers manage all the stages of IF from onset to ITx, including home-PN program(2,70,71). SBS remains the most common indication for intestinal Tx accounting for 63% versus 32% in our transplantation centre(68,69).

Liver consequences of poor functioning remnant small intestine with intestinal stasis and subsequent sepsis from bacterial overgrowth might be prevented by appropriate medico-surgical approach. 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).

Development of integrated centers involved in all stage of IF management should be encouraged. They must have a high level of expertise in the fields of Pediatric Gastroenterology and Clinical Nutrition with a well organized Home-PN program, together with experienced pediatric surgeons involved in SBS non-transplant surgery as well as in intestinal transplantation(72-75). ITx offers not only an improved quality of life but maintains optimal nutritional status(76-80).

**Conclusion**

To conclude, long-term home parenteral nutrition is the primary therapeutic option for intestinal failure. Irreversible IF should be identified among patients with IF. Patients with IF related complications, according to the U.S.A. Medicaid and Medicare indication are candidate for ITxs. IF-related liver failure is the one associated with the highest risk of death before transplantation. ITx cannot be life-saving if the transplant comes too late, when the patient, clinical status is severely compromised. Strategies are needed to prevent the development of liver failure and to objectively define the optimal timing for ITx in patients having irreversible intestinal failure. Intestinal transplantation should now move from a life saving to a life enhancing procedure, thanks to the development of IF rehabilitation centers.

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