# CURRENT ISSUES IN INTESTINAL FAILURE IN CHILDREN – CAUSES AND MANAGEMENT

**Elena D Serban, Oana Maftei**
Pediatric Clinic II, Emergency Hospital for Children
University of Medicine and Pharmacy „Iuliu Haţieganu", Cluj-Napoca

**Abstract**

The concept of intestinal failure (IF) is currently defined as a critical reduction of functional gut mass below the minimum amount necessary for adequate digestion and absorption to satisfy body nutrient and fluid requirements for growth in children or maintenance in adults. Causes of IF include intestinal hypomotility disorders, intestinal mucosal disorders, and the short bowel syndrome. We present the actual possibilities in the management of the IF – enteral and parenteral nutrition, non-transplant surgery and intestinal transplantation, analysing their indications, contraindications, and complications.

**Key words:** intestinal failure, parenteral nutrition, intestinal transplantation, child

*DEFINITION OF INTESTINAL FAILURE:*

The concept of intestinal failure (IF) is currently defined as a critical reduction of functional gut mass below the minimum amount necessary for adequate digestion and absorption to satisfy body nutrient and fluid requirements for growth in children or maintenance in adults[1]. According to the recent consensus of the IF Working Group, IF is characterized by the inability of the body to maintain the balance of proteins, energy, electrolytes or micronutrients[2,3]. The real incidence and prevalence of IF are not known[4]. If children on home parenteral nutrition (PN) are taken into account, the incidence of IF in the general population is 2-6.8/1 million[5]. The incidence of short bowel syndrome (SBS) in the general population is 2-5/1 million[6].

*CAUSES OF INTESTINAL FAILURE:*

a) Intestinal motility disorders[4]: chronic intestinal pseudo-obstruction[1,4], Hirschprung disease – especially the rare form of total aganglionosis with jejuno-ileal involvement[1];
b) Intestinal mucosal disorders[4]: primary epithelial abnormalities[7] (epithelial dysplasia, microvillous inclusion disease, congenital disorders of glycosylation) and immune mediated disorders (severe combined immunodeficiency, severe hypogammaglobulinaemia, autoimmune enteropathy with nephropathy, unclassified autoimmune enteropathy);
c) Short bowel syndrome – following extensive intestinal resections with reduction of functional gut mass[1]:
   - in neonates: gastroschisis, necrotising enterocolitis, small bowel atresia, malrotation with volvulus[4], mesenteric arterial and venous thrombosis[1];
   - after the neonatal period: Crohn's disease, radiation enteritis, tumors, trauma, mesenteric infarction[4], extensive angioma[1], arterial thrombosis[1], complicated intussusception[1].

In *children*, SBS is the most common indication for long-term PN[1]. Intestinal resections can be either short (leaving 100-150 cm of small intestine), large (leaving 40-100 cm) or massive (leaving less than 40 cm)[1]**.** The age at the time of resection, degree of cholestasis (IF associated liver disease), type of the small bowel remaining (ileum adapts better than jejunum), residual length of the small bowel, preservation of the ileo-caecal valve, preservation of at least the right colon, functional integrity of the remaining small intestine, and early establishment of intestinal continuity are all factors that are considered very important for adaptation[1]. The *time* of resection is also essential because at birth, the small bowel is 250 ± 40 cm long and its increase in length is maximal during infancy[8]. It doubles its length during the last trimester of pregnancy, which accordingly confers a benefit of full-term birth compared to a premature birth[8].

In summary, *the favourable factors for intestinal adaptation are therefore residual small bowel longer than 15 cm, presence of the ileo-caecal valve, preservation of the colon and the functional integrity of the remnant intestine*[9]. But the residual intestine may become dilated and dysmotile, leading to stasis of intestinal nutrients and small bowel bacterial overgrowth (SBBO). SBBO may lead to malabsorption and bacterial translocation, with potential sepsis[4]. SBBO is more likely to occur in the case of ileo-caecal resection[1]. In addition, SBBO exacerbates hepatotoxicity related to PN[9].

*CLASSIFICATION OF INTESTINAL FAILURE:*

With so many causes, IF may have various degrees of severity and duration[3].

a) According to the duration, IF may be acute (reversible within 6 months) or chronic (longer than 6 months, and even permanent)[3];
b) According to the type (this classification has been established in adults)[10]:

- type 1: self-limiting IF – usually following abdominal surgery
- type 2: IF in severely affected patients with extensive intestinal resections, with septic, metabolic and nutritional complications, and necessitating a multidisciplinary approach
- type 3: chronic IF – patients need long-term PN.

*MANAGEMENT OF INTESTINAL FAILURE:*

A multidisciplinary approach[11,12] is mandatory, including a pediatric gastroenterologist, pediatric surgeon, surgeon specialized in liver and intestinal transplantation, dietician, PN pharmacist, social nurse, and nutritional nurse.

*A. MANAGEMENT OF SHORT BOWEL SYNDROME*

*I. Medical management*

Parenteral nutrition is the cornerstone of management, promoting normal growth in children with SBS[1]. The duration of PN varies according to the residual intestine length and the presence of the ileo-caecal valve[1].

Following resection, enteral nutrition (EN) is the most important factor in promoting intestinal adaptation and intestinal hyperplasia[4]. Therefore, early oral feeding/enteral nutrition is recommended, leading to enhancement of gastrointestinal secretion, salivary epidermal growth factor and gallbladder motility[9]. Breast milk with its trophic factors, such as epidermal growth factor, is the best choice in the first few months of life[13]. Conceptually, a protein hydrolysate or amino acid based formula seems to be more appropriate in patients with SBS due to the decreased luminal contact time, but there is no convincing evidence to support their use in preference to a polymeric feed[4] (amino acids would be only less antigenic[13]). Some children have disaccharide intolerance and a glucose polymer based formula may be used[4]. A high fat diet (60% of the calories) may be beneficial (providing energy) and does not have a significant impact on stool volume or losses in children with an end-jejunostomy[14].

Continuous nasogastric feeding initially, followed by overnight nasogastric feeding and bolus feeding during the day, is recommended in order to use the residual small bowel function and to encourage oral feeding[4]. It is important to maintain a urinary sodium/potassium ratio of at least 2:1 with an absolute urinary sodium concentration of over 10-20 mmol/l in children with significant fluid and electrolyte losses[14].

Currently, there is no convincing evidence to support the routine use of pectin, glutamine, growth hormone, or IGF-1 as trophic factors in the process of intestinal adaptation[15]. A promising agent in the promotion of intestinal adaptation is glucagon-like peptide-2 (GLP-2), a pro-glucagon derived peptide secreted from the ileal and colonic mucosa after feeding[16]. GLP-2 induces marked proliferation of the small intestine epithelium in patients with SBS, increasing body weight and nutrient absorption[16].

Various *antibiotic* regimens can be used for 7 to 14 days, with 14 to 28 days of interruption[17], but very cautiously to preserve the intestinal bacterial flora for production of short chain fatty acids and/or avoid the emergence of multiresistant strains of bacteria[1]. Metronidazole (10-20 mg/kg/day) can be used, either alone or in association with trimethoprim-sulfamethoxazole.

*Probiotics* might be helpful, although there is no significant evidence for this in children[18].

*II. Surgery*

Besides *intestinal transplantation (IT)*, non-transplant surgery can be used to provide maximum mucosal contact without disturbing motility or reducing total absorptive mass[4]. The Bianchi procedure (bowel lengthening), intestinal plication or tapering and the serial transverse enteroplasty procedure (STEP) are examples of such methods[11].

Patients with dilated bowel segments need to meet some anatomical criteria in order to be selected for longitudinal intestinal lengthening and tailoring, including intestinal diameter > 3 cm, length of residual small bowel > 40 cm and length of dilated bowel > 20 cm[1]. The STEP procedure has some advantages over the Bianchi procedure, since the intestinal blood supply remains undisturbed, and it can be performed on smaller dilated segments as well as on dilated bowel segments after a previous Bianchi procedure[4]. They are effective especially in children with mild liver disease and without significant portal hypertension, and can be performed also after liver transplantation[1].

*B. PARENTERAL NUTRITION*

PN can be partial or total, temporary (helpful for SBS) or permanent (for intestinal motility disorders and intestinal mucosal disorders)[4]. After 4 years, the survival rate in patients with home PN is 80% for SBS and 70% for motility disorders. Some complications can be encountered associated with long term use of PN: central venous catheter related infections; thrombosis leading to impaired venous access[4]; intestinal failure associated liver disease (IFALD) – expression that replaces the old name of parenteral nutrition associated liver disease[1]; and bone disease (dual-energy X-ray absorptiometry, as well as phosphorus and calcium serum levels should be assessed)[1]. In a recent study, the following *complications* of total PN were reported: complications associated with the central venous catheter (mechanical – 52%, infectious – 26%), metabolic (3%) and hepatic (19%) complications[22].

- *Central venous catheter related infections (potentially leading to sepsis)* – can cause a rise in bilirubin level of higher than one third and cholestasis may develop in 90% of infants after the first infection. *Frequent infections may contribute to progressive liver disease*[23].
- *Vascular thrombosis* – the repeated episodes of line infections with multiple surgical procedures to remove and insert catheters may predispose to thrombosis[24]. Percutaneous vascular insertion techniques using Doppler ultrasound, with minimal trauma, may be more helpful[25]. It seems that the use of anticoagulants for prevention of vascular thrombosis is not beneficial[26]. Pulmonary thromboembolism occurs in 39% of the children, and have a fatal potential[27]. In asymptomatic children yearly echocardiography and ventilation-perfusion scanning are recommended[4].
- *IFALD* – occurs in 40-60% of the infants on long term PN (versus 15-40% in adults on home PN)[28]. In a recent study, IFALD occurs in 25% of the children on home PN[29].

IFALD includes steatosis, cholestasis, hepatic fibrosis and cholelithiasis[28]. Progression of liver disease towards biliary cirrhosis, portal hypertension and hepatic failure occurs in a minority of patients, but it is more common in newborns and infants than in adults[28]. Abnormalities in hepatic enzymes are often seen within the

first four weeks of onset of PN in children[4]. Due to the risk for development of gallstones, abdominal ultrasound is recommended twice a year[1].

Multiple factors are involved in the pathogenesis of IFALD[28]:

- *in infants*: *prematurity, low birth weight, duration of PN, repeated laparotomies* for SBS, recurrent *sepsis*, and direct hepatotoxicity due to the *hepatic immaturity*; in addition, premature babies also present deficiencies of *taurine or cysteine*;
- other important mechanisms include:
  - ❖ deficiency of choline (at any age), associated with steatosis and cholestasis[28];
  - ❖ absence of enteral nutrition (leading to a reduction of intestinal hormones[28] and, following intestinal resections, to a decrease of the enterohepatic circulation and of biliary flow, thus promoting cholestasis and the accumulation of toxic bile acids causing cholestasis[4]);
  - ❖ SBBO, catheter infections release endotoxin and pro-inflamatory mediators[1];
  - ❖ lipids (notably polyunsaturated fatty acids)[1]; generally, high level of serum lipids is associated with IFALD[4];
  - ❖ aluminium, chromium or iron overload;
  - ❖ magnesium toxicity (at any age), associated with steatosis and cholestasis[28];
- in *adults*, IFALD is less common and varies with age, duration of PN, energy intake, excessive intake of lipids or glucose.

*Prevention* of IFALD requires:

- a multidisciplinary approach to management of PN
- stimulation of early enteral nutrition[1]
- use of aseptic catheters to reduce the incidence of sepsis
- supplementation of PN with choline, taurine and cysteine
- reduction of iron and aluminium intake in the solutions for PN[1]
- oral ursodesoxycholic acid (30 mg/kg/day) to improve bile flow and reduce biliary stasis[28]
- use of appropriate intravenous fat emulsions (not more than 2[1]-2,5 g/kg/day), containing various combinations of medium and long chain tryglicerides[4]
- control of the lipid supply and rate of delivery, including stopping intravenous lipids as soon as thrombocytopenia, hyperbilirubinemia and/or jaundice appear[1]
- ingestion of long-chain tryglicerides, breast milk[1], or injection of cholecystokinin analogs[30], for stimulation of the enterobiliary axis
- limiting glucose intake[1,4] to prevent insulin resistance and hepatic steatosis[17]
- performing cyclic PN (instead of continuous PN) thereby reducing hyperinsulinism and liver steatosis[31].

*Prognosis* of IFALD is correlated to the rapid progression of the disease, requiring early intestinal transplantation. Children referred with a plasma bilirubin concentration of higher than 200 µmol/l have a life expectancy without intestinal transplantation of 6 months. In children with cirrhosis, survival at 12 months is 30%. The development of coagulopathy and portal hypertension with varices reduces survival to less than 8 weeks[33]. In patients with SBS, isolated liver transplantation may be performed[33].

### C. *INTESTINAL TRANSPLANTATION (ITx)*

Small bowel transplantation is a salvage procedure for those patients with IF where total PN is not efficient and/or has severe side effects[34]. In July 2005 more than 1300 ITx have been performed worldwide in 65 centres in 19 countries[4].

The *indications* for ITx are *irreversible IF* (requiring parenteral intake of more than 50% of calories) despite all medical and/or surgical attempts at digestive autonomy (discontinuation of PN), and associated with one of the following conditions[21,35]:

- ♦ vascular thrombosis with impaired venous access (more than 2 thrombosis in the subclavian, jugular or femoral veins)[34];
- ♦ progressive liver disease[34] (with coagulopathy, bilirubin levels over 3 mg%, splenomegaly, gastroesophageal varices, thrombocytopenia, ascites and encephalopathy);
- ♦ severe, recurrent catheter-related sepsis[34] (2 episodes of sepsis per year, 1 episode of line-related fungemia, septic shock or acute respiratory distress syndrome);
- ♦ metabolic disorders that are ineffectively treated with PN and that affect the growth of the child
- ♦ underlying disease leading to uncontrollable water-electrolyte losses, recurrent severe acute dehydration (life-threatening condition if PN is not used after 24 hours) – e.g. intractable diarrhoea[21,35].

*Factors* influencing the survival of children with IF referred for ITx include[33] age below 1 year, surgical disease, bridging fibrosis and cirrhosis, bilirubin levels over 3 mg% and thrombocytopenia.

*Contraindications* to ITx are[4]:

- ♦ absolute: severe neurological disorders, non-resectable malignancies, and life-threatening or other irreversible diseases unrelated to the digestive system,
- ♦ relative: severe congenital or acquired immunological deficiencies, multisystem autoimmune diseases, insufficient vascular patency to guarantee vascular access for up to 6 months after transplant, and chronic lung disease of prematurity.

There are several *types of operation*[4]:

- ♦ isolated ITx (in patients with mild liver disease – no evidence of portal hypertension, mild hepatic fibrosis on biopsy)
- ♦ small bowel and liver transplant (in patients with moderate to severe liver disease)
- ♦ multivisceral transplantation (more than the liver and small bowel are transplanted, usually stomach and whole pancreas) – in patients with extensive disease, e.g. motility disorders or desmoid tumours.

The preferred technique is the composite graft where the liver and intestine with bile ducts, duodenum and the head of pancreas can be implanted en bloc with minimal disruption to the vascular and other structures connecting the organs, or the organs can be retrieved from the donor,

separated and implanted individually (non-composite combined liver and small bowel transplantation). Statistical reports show that small bowel transplant (± colonic) represents 44% of grafts, liver and intestinal transplantation 48%, while multivisceral transplantation (small bowel, stomach, pancreas, and liver) make up 11%[36]. Due to the lack of availability of size-matched organs, 50-60% of the children die on the ITx waiting list, the majority of these being infants and less than 10 kg weight. In order to overcome this problem, the technique of en bloc reduction can be performed, using the liver and small bowel from much larger adult donors, by excision usually the right lobe of the liver and mid-section of the small bowel graft. Graft survival at 1 year increased to 65% for isolated ITx and to 59% for liver and intestinal transplantation[34]. Overall survival at 5 years after isolated ITx or liver and intestinal transplantation is 50%[28].

ITx related c*omplications* were common in the past and included significant surgical morbidity, moderate to severe acute rejection and opportunistic infections[4,36]. The incidence and severity of rejection has improved considerably after the advent of IL-2 blockers and other immunosuppression strategies[4,36]. Generally, following transplant forms of induction (thymoglobulin, IL-2 receptor antagonists) and maintenance (tacrolimus) therapies need to be used[34]. Tacrolimus is the most widely used drug to prevent rejection (in 75% of the patients)[34]. Studies have shown that rejection rate is lower in liver and intestinal transplantation. Currently, rejection, bacterial, fungal and viral (Cytomegalovirus, Epstein-Barr-virus) infections, post-transplant lymphoproliferative disease and graft versus host disease are the most common complications after intestinal transplantation. However, with the use of an appropriate cytomegalovirus prophylaxis regimen and Epstein-Barr virus polymerase chain reaction monitoring techniques for prevention of neoplastic post-transplant lymphoproliferative disease, the incidence of these complications decreased significantly[36].

In the experience of Birmingham Children's Hospital, 212 children with IF were assessed for ITx between 1989 and 2005. They were categorised into three prognostic groups: stable on PN (n=82); unsuitable for transplantation (n=43) due to end stage liver disease and/or other co-morbid conditions; or recommended for transplantation (n=87). Of the 87 children recommended for transplantation, 9 families declined ITx, 22 children died on the waiting list, 2 children improved, while 38 ITx (median age 2.3 years, median weight 11 kg) and 16 intestinal and liver transplantation (median age 0.8 years, median weight 7.8 kg) were performed[4]. In 2006, 18 of 38 children with ITx and 9 out of 14 isolated liver transplant children were still alive (overall 5 year survival rate of 52%)[4]. There is evidence that quality of life in 10-16 year old ITx recipients is similar to healthy children, although their parents remained more anxious than the parents of healthy children[38].

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Correspondence to:
Elena D Serban,
Pediatric Clinic II,
Emergency Hospital for Children
Cluj-Napoca,
Romania,
E-mail: danitiserban@yahoo.com