Permanent Intestinal Failure

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ABSTRACT

Context*: Intestinal failure (IF) requires the use of parenteral nutrition as long as it persists and may be in case of persistence an indication for intestinal transplantation.* ***Evidence acquisition:*** *Literature search was performed both electronically and manually.* ***Results and conclusions:*** *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 available to date. Data on morbidity and mortality in pediatric patients with SBS are very limited while long-term outcome seems 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 centers involving pediatric surgery, pediatric gastroenterology, parenteral nutrition expertise, home- parenteral nutrition program, and liver-intestinal transplantation experience. Timing for referral of patients in specialized centers remains a crucial issue. The main causes of IF are briefly reviewed emphasizing the medico-surgical strategy for prevention and care-provision, adapted to each type and stage of IF.*

Key words: *Citrulline, Congenital enteropathy, Chronic intestinal pseudoobstruction, Intestinal failure, Intestinal transplantation, Liver transplantation, Parenteral nutrition, Short bowel syndrome.*

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 functional gut 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

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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* I)(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.

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%
Necrotising enterocolitis	27%	14%	35%	43%

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).

Small bowel bacterial overgrowth (SBBO) is a frequent complication that is likely to occurr 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 enterobiliary 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 provison and cyclic infusion(3). The recentlly 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;

KEY MESSAGES

- Intestinal failure results from the critial 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.

(*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 nutrional 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

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.

INTESTINAL 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 ITx. 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.

REFERENCES

1. Goulet O, Sauvat F. Short bowel syndrome and intestinal transplantation in children. Curr Opin Clin Nutr Metab Care 2006; 9: 304-313.

2. Colomb V, Dabbas-Tyan M, Taupin P, Talbotec C, Révillon Y, Jan D, *et al.* Long-term outcome of children receiving home parenteral nutrition: a 20-year single-center experience in 302 patients. J Pediatr Gastroenterol Nutr 2007; 44: 347-353.

3. Goulet O, Ruemmele F. Causes and management of intestinal failure. Gastroenterol 2006;130: 516-528.

4. Crenn P, Vahedi K, Lavergne-Slove A, Cynober L, Matuchansky C, Messing B. Plasma citrulline: A marker of enterocyte mass in villous atrophy-associated small bowel disease. Gastroenterol 2003; 124: 1210-1219.

5. David AI, Gaynor JJ, Zis PP, Conanan L, Goldsmith L, Esquenazi V, *et al*. An association of lower serum citrulline levels within 30 days of acute rejection in patients following small intestine transplantation. Transplant Proc 2006; 38: 1731-1732.

6. Jianfeng G, Weiming Z, Ning L, Fangnan L, Li T, Nan L, *et al*. Serum citrulline is a simple quantitative marker for small intestinal enterocytes mass and absorption function in short bowel patients. J Surg Res 2005; 127: 177-182.

7. Rhoads JM, Plunkett E, Galanko J, Lichtman S, Taylor L, Maynor A, *et al*. Serum citrulline levels correlate with enteral tolerance and bowel length in infants with short bowel syndrome. J Pediatr 2005; 146: 542-547.

8. Koffeman GI, van Gemert WG, George EK, Veenendaal RA. Classification, epidemiology and aetiology. Best Pract Res Clin Gastroenterol 2003; 17: 879-893.

9. Goulet O, Baglin-Gobet S, Talbotec C, Fourcade L, Colomb V, Sauvat F, *et al*. Outcome and long-term growth after extensive small bowel resection in the

neonatal period: a survey of 87 children. Eur J Pediatr Surg 2005 ; 15: 95-101.

10. Wales PW, de Silva N, Kim JH, Lecce L, Sandhu A, Moore AM Neonatal short bowel syndrome: a cohort study. J Pediatr Surg 2005; 40: 755-762.

11. Andorsky DJ, Lund DP, Lillehei CW, Jaksic T, Dicanzio J, Richardson DS, *et al*. Nutritional and other postoperative management of neonates with short bowel syndrome correlates with clinical outcomes. J Pediatr 2001; 139: 27-33.

12. Diamond IR, de Silva N, Pencharz PB, Kim JH, Wales PW; Group for the Improvement of Intestinal Function and Treatment. Neonatal short bowel syndrome outcomes after the establishment of the first Canadian multidisciplinary intestinal rehabilitation program: preliminary experience. J Pediatr Surg 2007; 42: 806-811.

13. Bin-Nun A, Bromiker R, Wilschanski M, Kaplan M, Rudensky B, Caplan M, *et al*. Oral probiotics prevent necrotizing enterocolitis in very low birth weight neonates. J Pediatr 2005; 147: 192-196.

14. Lin HC, Su BH, Chen AC, Lin TW, Tsai CH, Yeh TF, *et al*. Oral probiotics reduce the incidence and severity of necrotizing enterocolitis in very low birth weight infants. Pediatrics 2005; 115: 1-4.

15. Deshpande G, Rao S, Patole S. Probiotics for prevention of necrotising enterocolitis in preterm neonates with very low birthweight: a systematic review of randomised controlled trials. Lancet 2007; 369 :1614-1620.

16. Quiros-Tejeira RE, Ament ME, Reyen L, Herzog F, Merjanian M, Olivares-Serrano N, *et al*. Long-term parenteral nutritional support and intestinal adaptation in children with short bowel syndrome: a 25-year experience. J Pediatr 2004;145 :157-163.

17. Spencer AU, Neaga A, West B, Safran J, Brown P, Btaiche I, *et al*. Pediatric short bowel syndrome: redefining predictors of success. Ann Surg. 2005; 242: 403-409.

18. Jackson CS, Buchman AL. The nutritional management of short bowel syndrome. Nutr Clin Care 2004; 7: 114-121.

19. Mitchell JE, Breuer RI, Zuckerman L, Berlin J, Schilli R, Dunn JK. The colon influences ileal resection diarrhea. Dig Dis Sci 1980; 25: 33-41.

20. Puwanant M, Mo-Suwan L, Patrapinyokul S. Recurrent D-lactic acidosis in a child with short bowel syndrome. Asia Pac J Clin Nutr 2005; 14: 195-198.

21. Kaufman SS, Loseke CA, Lupo JV, Young RJ, Murray ND, Pinch LW, *et al*. Influence of bacterial overgrowth and intestinal inflammation on duration of PN in children with short bowel syndrome J Pediatr 1997: 131: 356-361.

22. Forchielli ML, Walker WA. Nutritional factors contributing to the development of cholestasis during total parenteral nutrition. Dev Pediatr 2003; 50: 245-267.

23. Matarese LE, Seidner DL, Steiger E. The role of probiotics in gastrointestinal disease. Nutr Clin Pract 2003; 18: 507-516.

24. Wales PW. Surgical therapy for short bowel syndrome. Pediatr Surg Int 2004; 20: 647-657.

25. Bianchi A. Longitudinal intestinal lengthening and tailoring: results in 20 children. J R Soc Med 1997; 90: 429-432.

26. DiBaise JK, Young RJ, Vanderhoof JA. Intestinal rehabilitation and the short bowel syndrome: part 2. Am J Gastroenterol 2004; 99: 1823-1832.

27. Javid PJ, Kim HB, Duggan CP, Jaksic T. Serial transverse enteroplasty is associated with successful short-term outcomes in infants with short bowel syndrome. J Pediatr Surg 2005; 40: 1019-1023.

28. Modi BP, Javid PJ, Jaksic T, Piper H, Langer M, Duggan C, *et al*. First report of the international serial transverse enteroplasty data registry: indications, efficacy, and complications. J Am Coll Surg 2007; 204: 365-371.

29. Seguy D, Vahedi K, Kapel N, Souberbielle JC, Messing B. Low-dose growth hormone in adult home PN-dependent short bowel patients: a positive study. Gastroenterology 2003; 124: 293-302.

30. Parekh NR, Steiger E. Criteria for the use of recombinant human growth hormone in short bowel syndrome. Nutr Clin Pract 2005; 20: 503-508.

31. Dabbas-Tyan M, Colomb V, Rosilio M, Landais P, Ricour C, Goulet O. Evaluation of the effect of recombinant human growth hormone (rhGH) treatment of children with short bowel syndrome. J Pediatr Gastroenterol Nutr 2000 ; 31 : 5165-5166

32. Lifschitz C, Duggan C, Lazngston C, Vanderhoof J, Shulman RJ. Growth Hormone (GH) therapy in children with short bowel syndrome (SBS): a

randomized, placebo controlled study. Digestive Disease Week; Orlando 2003: A100.

33. Jeppesen PB, Sanguinetti EL, Buchman A, Howard L, Scolapio JS, Ziegler TR, *et al*. Teduglutide (ALX-0600), a dipeptidyl peptidase IV resistant glucagon-like peptide 2 analogue, improves intestinal function in short bowel syndrome patients. Gut 2005; 54: 1224-1231.

34. Sigalet DL, Martin G, Meddings J, Hartman B, Holst JJ. GLP-2 levels in infants with intestinal dysfunction. Pediatr Res 2004; 56: 371-376.

35. Iskit SH, Tugtepe H, Ayyildiz SH, Kotiloglu E, Dagli TE, Yegen BC. Epidermal growth factor and bombesin act synergistically to support intestinal adaptation in rats with massive small bowel resection. Pediatr Surg Int 2005; 21: 436-440.

36. Sigalet DL, Martin GR, Butzner JD, Buret A, Meddings JB. A pilot study of the use of epidermal growth factor in pediatric short bowel syndrome. J Pediatr Surg 2005; 40: 763-768.

37. Sukhotnik I, Mogilner J, Shamir R, Shehadeh N, Bejar J, Hirsh M, Coran AG. Effect of subcutaneous insulin on intestinal adaptation in a rat model of short bowel syndrome. Pediatr Surg Int 2005; 21: 132-137.

38. Sukhotnik I, Shehadeh N, Shamir R, Bejar J, Bernshten A, Mogilner JG. Oral enhances intestinal re-growth following massive resection in rat. Dig Dis Sci 2005; 50: 2379-2385.

39. Sauvat F, Grimaldi C, Lacaille F, Ruemmele F , Dupic L, Bourdaud N, *et al*. Intestinal transplantation for total intestinal aganglionosis : A series of twelve consecutive children. J Pediatr Surg 2008 (in press).

40. Faure C, Goulet O, Ategbo S, Breton A, Tounian P, Ginies JL, *et al*. Chronic intestinal pseudoobstruction syndrome: clinical analysis, outcome and prognosis in 105 children. Dig Dis Sci 1999; 44: 953-959.

41. Heneyke S, Smith VV, Spitz L, Milla PJ. Chronic intestinal pseudo-obstruction : treatment and long term follow up of 44 patients. Arch Dis Child 1999 ; 81 : 21-27.

42. Loinaz C, Mittal N, Kato T, Miller B, Rodriguez M, Tzakis A. Multivisceral transplantation for pediatric intestinal pseudo-obstruction: single center's experience of 16 cases. Transplant Proc 2004; 36: 312-313.

43. Masetti M, Di Benedetto F, Cautero N, Stanghellini V, De Giorgio R, Lauro A, *et al*. Intestinal transplantation for chronic intestinal pseudo-obstruction in adult patients. Am J Transplant 2004; 4: 826-829.

44. Ruemmele FM, Schmitz J, Goulet O. Microvillous inclusion disease (microvillous atrophy).Orphanet J Rare Dis 2006; 1: 22.

45. Goulet O, Kedinger M, Brousse N, Cuenod B, Colomb V, Patey N, *et al*. Intractable diarrhea of infancy: a new entity with epithelial and basement membrane abnormalities. J Pediatr 1995; 127 : 212-219.

46. Goulet O, Salomon J, Ruemmele F, Patey-Mariaud de Serres N, Brousse N. Intestinal epithelial dysplasia (Tufting enteropathy). Orphanet J Rare Dis 2007; 2: 20.

47. Randak C, Langnas AN, Kaufman SS, Phillips AD, Wisecarver JL, Hadorn HB, *et al*. Pretransplant management and small bowel-liver transplantation in an infant with microvillus inclusion disease. J Pediatr Gastroenterol Nutr 1998; 27:333-337.

48. Oliva MM, Perman JA, Saavedra JM, Young-Ramsaran J, Schwarz KB. Successful intestinal transplantation for microvillus inclusion disease. Gastroenterology 1994 ; 106 : 771-774.

49. Lacaille F, Cuenod B, Colomb V, Jan D, Canioni D, Revillon Y, *et al*. Successful combined liver and small bowel transplantation in a child with epithelial dysplasia. J Pediatr Gastroenterol Nutr 1998; 27: 230-233.

50. Goulet O, Sauvat F, Ruemmele F, Caldari D, Damotte D, Cezard JP, *et al*. Results of the Paris program: ten years of pediatric intestinal transplantation. Transplant Proc 2005; 37:1667-1670.

51. Ruemmele F, Jan D, Lacaile F, Cezard JP, Canioni D, Phillips AD, *et al*. New perspectives for children with microvillous inclusion disease: early small bowel transplantation. Transplantation 2004; 77: 1024-1028.

52. Ruemmele FM, Brousse N, Goulet O. Autoimmune enteropathy. *In*: Walker A, Goulet O, Kleinman R, Shneider P, Sherman P, Sanderson I. Pediatric Gastrointestinal Disease. Hamilton, Ontario, Canada: BcDecker Inc Publisher; 2004. p. 959-965.

53. Wildin RS, Smyk-Pearson S, Filipovich AH.

Clinical and molecular features of the immuno-dysregulation, polyendocrinopathy, enteropathy, and X-linked (IPEX) syndrome. J Med Genet 2002; 39: 537–545.

54. Bindl L, Torgerson T, Perroni L, Youssef N, Ochs HD, Goulet O, *et al*. Successful use of the new immune-suppressor sirolimus in IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome). J Pediatr 2005; 147: 256-259.

55. Baud O, Goulet O, Canioni D, Le Deist F, Radford I, Rieu D, *et al.* Treatment of the immune dysregulation, polyendocrinopathy, enteropathy, and X-linked syndrome (IPEX) by allogeneic bone marrow transplantation. N Engl J Med 2001; 344: 1758–1762.

56. Torgerson TR, Linane A, Moes N, Anover S, Mateo V, Rieux-Laucat F, *et al*. Severe food allergy as a variant of IPEX syndrome caused by a deletion in a noncoding region of the FOXP3 gene. Gastroenterology 2007; 132: 1705-1717.

57. Koletzko B, Goulet O, Hunt J, Krohn K, Shamir R; for the Parenteral Nutrition Guidelines Working Group. Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). J Pediatr Gastroenterol Nutr 2005; 41: S1-S4.

58. Hermans D, Talbotec C, Lacaille F, Goulet O, Ricour C, Colomb V. Early central catheter infections may contribute to hepatic fibrosis in children receiving long-term parenteral nutrition. J Pediatr Gastroenterol Nutr 2007; 44: 459-463.

59. Horslen SP, Sudan DL, Iyer KR, Kaufman SS, Iverson AK, Fox IJ, *et al*. Isolated liver transplantation in infants with end-stage liver disease associated with short bowel syndrome. Ann Surg 2002; 235: 435-439.

60. Botha JF, Grant WJ, Torres C, Iverson AK, Sudan DL, Shaw BW Jr, *et al.* Isolated liver transplantation in infants with end-stage liver disease due to short bowel syndrome. Liver Transpl 2006;12: 1062-1066.

61. Pironi L, Hébuterne X, Van Gossum A, Messing B, Lyszkowska M, Colomb V, *et al*. Candidates for intestinal transplantation: a multicenter survey in Europe. Am J Gastroenterol 2006;101: 1633-1643.

62. American Gastroenterological Association Medical Position Statement. Short bowel syndrome and intestinal transplantation. Gastroenterology 2003;124: 115-1110.

63. Buchman AL, Scolapio J, Fryer J. AGA technical review on short bowel syndrome and intestinal transplantation. Gastroenterology 2003; 124: 1111-1134.

64. Kaufman SS, Atkinson JB, Bianchi A, Goulet OJ, Grant D, Langnas AN, *et al*. Indications for pediatric intestinal transplantation: a position paper of the American Society of Transplantation. Pediatr Transpl 2001; 5; 80-87.

65. Colomb V, Jobert-Giraud A, Lacaille F, Goulet O, Fournet JC, Ricour C. Role of lipid emulsions in cholestasis associated with long-term PN in children. J Parenter Enteral Nutr 2000; 24: 345-350.

66. Bueno J, Ohwada S, Kocoshis S, Mazariegos GV, Dvorchik I, Sigurdsson L, *et al*. Factors impacting the survival of children with intestinal failure referred for intestinal transplantation. J Pediatr Surg 1999; 34: 27–33.

67. Fryer J, Pellar S, Ormond D, Koffron A, Abecassis M. Mortality in candidates waiting for combined liver-intestine transplants exceeds that for other candidates waiting for liver transplants. Liver Transpl 2003; 9 : 748-753.

68. Grant D, Abu-Elmagd K, Reyes J, Tzakis A, Langnas A, Fishbein T, *et al.;* Intestine Transplant Registry. 2003 report of the Intestine Transplant Registry : a new era has dawned. Ann Surg 2005; 241: 607-613.

69. Sauvat F, Dupic L, Caldari D, Lesage F, Cézard JP, Lacaille F, *et al*. Factors influencing outcome after intestinal transplantation in children. Transplant Proc 2006; 38: 1689-1691.

70. Lloyd DA, Vega R, Bassett P, Forbes A, Gabe SM. Survival and dependence on home parenteral nutrition: experience over a 25-year period in a UK referral centre. Aliment Pharmacol Ther 2006; 24: 1231-1240.

71. Guidelines on paediatric parenteral nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN). Home parenteral nutrition in children. J Pediatr Gastroenterol Nutr 2005; 41 Suppl 2, S70-S75.

72. Chungfat N, Dixler I, Cohran V, Buchman A, Abecassis M, Fryer J. Impact of parenteral nutrition-associated liver disease on intestinal transplant waitlist dynamics. J Am Coll Surg 2007; 205: 755-761.

73. Torres C, Sudan D, Vanderhoof J, Grant W, Botha J, Raynor S, *et al*. Role of an intestinal rehabilitation program in the treatment of advanced intestinal failure. J Pediatr Gastroenterol Nutr 2007; 45: 204-212.

74. Lopushinsky SR, Fowler RA, Kulkarni GS, Fecteau AH, Grant DR, Wales PW. The optimal timing of intestinal transplantation for children with intestinal failure: a Markov analysis. Ann Surg 2007; 246:1092-1099.

75. Nucci A, Cartland Burns R, Armah T, Lowery K, Yaworski JA, Strohm S, *et al*. Interdisciplinary Management of Pediatric Intestinal Failure: A 10-Year Review of Rehabilitation and Transplantation. J Gastrointest Surg 2008; 12: 429-436.

76. Sudan D. Cost and quality of life after intestinal transplantation. Gastroenterology 2006; 130: S132-137.

77. Venick RS, Farmer DG, Saikali D, Gordon S, Colangelo J, Reyen L, *et al*. Nutritional outcomes following pediatric intestinal transplantation. Transplant Proc 2006; 38:1718-1719.

78. Ueno T, Kato T, Revas K, Gaynor J, Velasco M, Selvaggi G, *et al*. Nutritional status after intestinal transplantation in children. Eur J Pediatr Surg 2006;16: 403-406.

79. Ueno T, Kato T, Revas K, Gaynor J, Velasco M, Selvaggi YO, *et al*. Growth after intestinal transplant in children. Transplant Proc 2006; 38: 1702-1704.

80. Lacaille F, Vass N, Sauvat F, Canioni D, Colomb V, Talbotec C, *et al.* Long-term outcome, growth and digestive function in children 2 to 18 years after intestinal transplantation. Gut 2007; 57; 455-461.