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Paediatric Intestinal Failure & Transplantation

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Abstract

Intestinal failure is a complex and debilitating condition characterised by inadequate small intestinal function requiring parenteral or intravenous nutrition to maintain health and, for children, to enable growth and development. Although parenteral nutrition can be prescribed in many hospitals, children with chronic intestinal failure have improved outcomes when managed at a paediatric centre by a multidisciplinary team with specialised expertise in the comprehensive management of intestinal failure. Recent advances in the medical, surgical and nutritional approach have been effective at optimising intestinal rehabilitation and achieving enteral autonomy while limiting complications of intestinal failure. The role of intestinal transplantation in the management of the child with intestinal failure continues to evolve as an option for children with life threatening complications of intestinal failure. The aim of this review is to highlight key advances in the care of children with intestinal failure.

Intestinal failure (IF) is a complex and debilitating condition characterised by inadequate small intestinal function requiring parenteral or intravenous nutrition (PN) to maintain health and, for children, to enable growth and development[1,2]. Advances in neonatal critical care and the surgical management of children with complex conditions has been associated with a significant increase in children with IF requiring home PN [3-5]. In the UK the rate of home PN in children has increased from 1.54 per million children in 2000 to 21.5 per million children in 2016 [5] . Although the number of patients is relatively small, it places a significant burden on affected children, their family, and the healthcare system[1,3,5,6]. Advances in intestinal rehabilitation and improvements in PN formulations and methods of safe administration mean many children who commenced PN in infancy now survive to adulthood [1,7,8]. The aim of this review is to highlight key recent advances in the care of children with IF.

Intestinal failure is classified functionally based on onset of the underlying disease, metabolic state and expected outcome (Table 1) [9]. The common underlying conditions resulting in IF differ in children from adults (Table 2) [1,3,8,9]. Short bowel syndrome (SBS) due to surgical resection is the most common cause of IF in children: about 30% of SBS is associated with neonatal necrotising enterocolitis[10]. The incidence of SBS in preterm infants (353.7 per 100,000 live births) is 100 times higher than in term infants (3.5 per 100,000)[11]. Congenital conditions requiring massive surgical resection with the development of SBS include intestinal atresia (duodenal, jejunal, ileal, or multiple intestinal atresias), abdominal wall defects (gastroschisis, omphalocoele), and intestinal malrotation with volvulus[2,3,8]. Approximately 20% of IF due to SBS occurs outside the neonatal period, predominantly secondary to volvulus or trauma[10]. Functional neuromuscular gut disorders, including chronic intestinal pseudo-obstruction, Hirschsprung disease, hollow visceral myopathy and megacystis microcolon intestinal peristalsis syndrome comprised 43% of home PN patients in a recent UK series[3,5,8]. With improved survival, children with cancer and severe immunological conditions associated with

extensive gastrointestinal mucosal inflammation are a growing cohort of home PN patients[3,5]. Another emerging group is children with neuro-disability associated with gastrointestinal dysmotility that interferes with enteral feeding, raising ethical concerns[3,12].

The impact of an expert multidisciplinary team

Although PN can be prescribed at many hospitals, management of children with chronic IF at a paediatric centre with specific expertise in IF management is recognised as an integral component of high quality care[1,3,13-16]. Critical decisions early in the course of management can have a long-term impact on the approach to care and patient outcome. A collaborative approach, involving a team experienced in acute and chronic management of patients with IF, can provide valuable input on the type or timing of surgical intervention, the placement of venous access devices, the prescribing of PN and other drugs and can provide important insights in family discussions and decision making. Focus of management often needs to be modified to respond to different phases of the disease and adapted at different stages of child development or in response to family or social factors. The composition of the team can vary between institutions, but a paediatric gastroenterologist, dietitian, nurse specialist and paediatric surgeon are frequent members of the team (Table 3)[1,15]. Benefits of the multidisciplinary team approach include reduced catheter related blood stream infections (11.5 to 1.1 CRBSI per 1000 catheter days)[17], improved survival (relative risk of 1.22; CI 1.04-1.42; p=0.005) and reduced costs[15,18].

Balancing nutritional needs while minimising risk of complications

Parenteral nutrition

Parenteral nutrition is a combination of water, electrolytes, amino acids, carbohydrates, fat and micronutrients aimed at providing for the age and development needs of the growing child. Balancing needs versus the potential for complications requires assessment and careful monitoring to ensure the PN provided is safe and effective and to detect any complications before they result in

clinical problems or become irreversible (Table 4). PN nutrient solutions are now available that reflect the specific nutritional needs of preterm and term infants and take into account developmental immaturity of some metabolic systems. These solutions have been developed to meet infant requirements and reduce the risk of toxicity encountered with PN solutions developed for adults and older children. The role of trace elements in supporting growth and development has been recognised and solutions specific for infants and children and adjusted for weight and age have been revised in line with evidenced-based research.[19]

Intestinal failure associated liver disease

Although it is a life-saving therapy for children with chronic IF, PN administration can be associated with severe, even fatal complications[1,15]. Long-term PN in children has been associated with cholestatic liver disease that may lead to fibrosis and end-stage liver disease[1,15,16]. Initially labelled PN-associated liver disease this complication is now known as intestinal failure associated liver disease (IFALD) in recognition of the multiple factors associated with the underlying requirement for PN. These factors include patient factors (prematurity, underlying disease, early diagnosis of sepsis, longer hospitalisation), nutrition factors (delayed or limited oral or enteral feeding, imbalance of PN nutrition, high lipid doses, soybean lipid emulsion, lipid peroxides), gastrointestinal factors (intestinal resection, bowel dysmotility and stasis, impaired bile acid recirculation, jejunostomy, small bowel overgrowth) and liver factors (pre-existing liver disease, drugs), see Table 4[1,13-16].

Focus on the potential role of intravenous fat emulsions on the pathogenesis and treatment of intestinal failure associated liver disease (IFALD) has led to the development of alternative fat emulsions as an option for the prevention and treatment of IFALD[20]. Intravenous soybean based lipid emulsions were initially implicated in the development of IFALD after it was observed that 70% (17 of 24) of the children normalised their bilirubin and 91% (11 of 12) of platelet counts returned

to normal after discontinuation of a soybean emulsion [20.] Possible explanations included phytosterol accumulation, oxidative stress with lipid peroxidation and activation of the reticuloendothelial system[20]. Composite and fish oil-based fat emulsions now provide an alternative for first line therapy or for specific indications in infants and children[21-23]. SMOF-lipid® (Fresnius Kabi: Graz, Austria) is composed of 30% soya bean oil (omega-6 fatty acid), 30% coconut oil (medium chain triglycerides), 25% olive oil (monounsaturated fatty acids) and 15% fish oil (omega-3 fatty acids) providing a balance of omega-6 to omega-3 polyunsaturated fatty acid ratio suitable for children, as well as anti-inflammatory effects provided by the fish oil and a lower phytosterol content. Children receiving SMOF-lipid® had lower serum bilirubin levels and higher serum docosahexaenoic acid, eicosapentaenoic acid and vitamin E levels compared to children who received a soybean emulsion[22]. SMOF-lipid® has been reported to lower serum bilirubin in children with jaundice after receiving a soybean emulsion[21]. Fish oil-based emulsion (Omegaven ®, Fresenius Kabi, Graz, Austria) has been proposed as a rescue agent to treat intestinal failure-associated liver disease[23]. Resolution of cholestasis has been reported in 50-82.5% of children treated with Omegaven (1g/kg/day)[23-26]. Long-term administration with Omegaven has been discouraged due to the risk of essential fatty acid deficiency, although this has not been consistently observed[27,28]. Until further information becomes available, Omegaven is recommended as a short- to intermediate-term therapy, specifically for patients at high risk of development of IFALD, or for treatment of those patients with established intestinal failure related liver disease [29].

Vascular access related complications

Central line associated bloodstream infections (CLABSI) are a major cause of death and hospitalisation in patients requiring long-term PN[8,15,30]. A protocol to prevent CLABSI reduced infection episodes in children with IF (1.7 to 0.7 per 1000 catheter days; p=0.018)[30]. Protection of catheters from occlusion, dislodgement or leakage is key to preservation of future vascular access options (Table 4). Strategies aimed at reducing biofilm development within the catheter through instillation of ethanol or

taurolidine-citrate locks have been associated with a reduction in CLABSIs (CLABSI rate per 100 catheter days: taurolidine-citrate lock 0.25 vs 4.16 with no lock) [30-32]. Thromboprophylaxis using low molecular weight heparin was associated with improved catheter free cumulative infection-free survival over 3 years (46% compared with 19%)[33].

The coming of age of intestinal rehabilitation

The importance of intestinal rehabilitation as a focus of management of children with IF has evolved over the past decade[1]. Paediatric intestinal rehabilitation centres have been established as regional or national referral centres specialising in the care of children with IF[1,8,15,16]. The aim of intestinal rehabilitation is to protect and promote gut function and achieve enteral autonomy while minimising the complications of IF (Table 4). Essential to success is providing balanced nutrition to support growth and development with a focus on optimising quality of life for children with IF and their family.

Promoting the transition from PN dependence to enteral nutrition and oral diet requires recognition of factors that enhance or hasten the natural process of adaptation that occurs after bowel resection or acute loss of gastrointestinal function[34]. This adaptation response is mediated by a broad range of factors acting independently or in combination (Table 4). The medical, surgical and nutritional approach to rehabilitation should be tailored to meet specific anatomical and functional characteristics of the gut, a range of patient and disease related factors and co-morbidities.

Small bowel bacterial overgrowth, common in children with IF,[15,35] is associated with delayed PN weaning, a reduced intestinal adaptive response and an increased risk of IFALD and CLABSI[35,36]. Gastrointestinal anatomical factors (gastroschisis, shorter residual bowel length), intestinal dysmotility and stasis and the use of acid suppressive therapy are linked with the development of small bowel bacterial overgrowth[35]. Clinical symptoms are often non-specific. Diagnosis by quantitative

culture of small intestinal aspirate is challenging in children[37]. The use of non-invasive surrogate markers such as urinary metabolic screen has shown promise when used in conjunction with a high level of clinical suspicion[37]. A combination therapeutic approach can include minimisation of gastric acid suppression, use of cycled enteral antibiotics and limiting dietary simple carbohydrates [35]. There is limited evidence to support the routine use of probiotics, which may also pose a risk of bacterial translocation and sepsis in patients with abnormal intestinal barrier function[35].

Autologous intestinal reconstruction surgery is aimed at restoring gut function, particularly in SBS with dilatation or dysmotility in the remnant segment resulting in refractory small bowel bacterial overgrowth[38]. Pioneered by Bianchi in the 1980's, the Bianchi technique or LILT involves longitudinal bowel lengthening and tailoring to increase intestinal absorptive area and reduce dilatation. The Serial Transverse EnteroPlasty (STEP) technique (lengthening and tapering using a stapler along the bowel), has been associated with a median increase in bowel length of 52.9%, with 42% of patients achieving enteral autonomy[39]. A recent modification of the STEP is the Spiral Lengthening and Tailoring (SILT) procedure which maintains the anatomical orientation of the muscle fibres of the intestine[38]. Used in combination with the STEP or as a primary reconstructive option in complicated SBS patients, SILT has shown promise in early reports[38].

The use of trophic hormones to reduce PN requirement in patients with IF has been heralded as a major advance in IF management (Table 4)[40,41]. GLP-2 is a 33 amino acid peptide, produced by the post-translation cleavage of proglucagon in the enteroendocrine L-cells of the intestine in response to nutrient intake. It acts via the GLP-2 receptor located in enteroendocrine cells, sub-epithelial myofibroblasts and neurons of the enteric nervous system and appears to stimulate gut hypertrophy, reduce gastric emptying and intestinal motility. GLP-2 has a half-life of minutes, so a GLP-2 analogue (teduglutide) with longer half-life has been developed[41]. In the pivotal trial of the GLP-2 analogue (Teduglutide) in adults, a 20% reduction in total

PN volume provided was achieved in 27/43 (63%) of adults receiving GLP-2 for 24 weeks compared to 13/43 (30%) receiving placebo ($p<0.01$)[41]. Improvement was associated with an increase in plasma citrulline, a marker of intestinal mucosal mass. On the basis of this and subsequent supportive data on long term use, teduglutide has been licensed internationally for the treatment of adults with SBS[41,42]. Data on the impact of teduglutide in children remains restricted to small numbers[43,44]. In children with SBS associated IF, teduglutide for 24 weeks (n=50) versus standard of care (n=9) was associated with a ≥20% reduction in administered PN volume in 13/24 (54%) and 18/26 (69%) patients receiving 0.025mg/kg or 0.05mg/kg teduglutide respectively compared to 1/9 (11%) receiving standard care[44]. PN calories, days per week and hours per day PN, and increased enteral nutrition was observed in children after 24 weeks' teduglutide therapy compared to baseline[44]. Five children receiving tedulgutide were able to wean from PN during the 24-week trial (10%). As clinical experience with teduglutide increases there is hope, at last, of an effective medical option to treat chronic IF without the need for PN. However, there remain unanswered questions such as whether life-long therapy will be required and safety considerations with long-term therapy, particularly for children. Cost is also likely to be a significant barrier.

Longterm outcomes in children with IF

Survival of children with IF has improved markedly, with transplant free survival for IF patients at most specialised programs reported at >90% [45]. Weaning from PN can be achieved in a significant proportion of SBS patients with chronic IF, even in the presence of very short bowel (<40cm)[1,7,8]. Factors predicting successful PN weaning in patients with SBS include longer residual small bowel length and preservation of the ileocaecal valve and/or colon [1,8]. As survival rates have improved there has been renewed focus on associated health-related outcomes and quality of life in children with IF and their family. Low bone mineral density was reported in 24.3% of children at a median age of 6 years, reduced to 16.2% when corrected for growth failure[46]. Children with IF are at risk of neurocognitive

problems, in particular children born preterm or with short bowel syndrome[6]. Poorer neurodevelopment outcomes were associated with ≥2 episodes of sepsis in the first year of life[47]. IF children may have decreased quality of life measures in physical, emotional and social life domains[6]. Parents of children with short bowel syndrome reported lower health-related quality of life and family relationships compared to parents of other chronically ill hospitalised children[6].

Intestinal transplantation

Intestinal transplantation has been restricted to children with irreversible intestinal failure suffering from life threatening complications of PN[48-50]. Transplant options include an isolated small intestine, combined small intestine and liver, and variations involving the stomach, colon, pancreas, kidney or a multi-visceral transplant. With the success of intestinal rehabilitation strategies, the number of paediatric intestinal transplants has decreased in the US from 1500 since 1985 to <50 transplants per year over the past decade[48]. Long-term outcomes have remained relatively stable over this period, overall 1-year and 5-year survival being 60% and 50% respectively, with better outcomes reported in experienced high-volume transplant centres [48]. The leading cause of death post-transplantation is sepsis although other long-term complications, such as chronic renal disease and lymphoproliferative disease, are not uncommon in transplant recipients[48]. Most children with a successful intestinal transplant are able to cease PN although supplemental enteral tube feeding is often still required[48].

Intestinal transplant listing criteria were recently revised to consider additional factors including home PN outcomes, quality of life and early referral to a transplant program and cost[48,49]. New disease indications include invasive intra-abdominal desmoids in adolescents and adults, acute diffuse intestinal infarction with hepatic failure and failure of first intestinal transplant. Refinements specific to children are persistent hyperbilirubinemia >75 micromol/L despite use of Omegaven lipid emulsion, presence of non-cholestatic IFALD with portal hypertension, thrombosis of 3 of 4

upper body central veins or occlusion of one brachiocephalic vein in children and life-threatening sepsis or other complications of intestinal failure necessitating 2 or more admissions to an intensive care unit[49,50]. The frequency and severity of co-morbidities remain an important factor influencing the decision to list individual patients for transplantation[48-50].

Conclusion

Intestinal failure (IF) is a complex and devasting condition. Children with IF have improved outcomes when managed at a paediatric centre with specific expertise. Over the past decade, there have been significant advances in medical and surgical approaches to intestinal rehabilitation with the development of centres of excellence in intestinal réhabilitation. The role of intestinal transplantation in the management of the child with IF continues to evolve as an option for children with life-threatening complications of IF.

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Conflict of Interest:

JEB and AR report no conflict of interest.

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References

1. Merritt RJ, Cohran V, Raphael BP, Sentongo T, Volpert D, Warner BW, Goday PS. Intestinal Rehabilitation Programs in the Management of Pediatric Intestinal Failure and Short Bowel Syndrome. *J Pediatr Gastroenterol Nutr* 2017;**65**:588-596.
2. Goulet O, Ruemmele F, Lacaille F, Colomb V. Irreversible intestinal failure. *J Pediatr Gastroenterol Nutr* 2004;**38**:250-69.
3. Lezo A, Capriati T, Immacolata Spagnuolo M, Lacitignola L, *et al.* Paediatric Home Artificial Nutrition in Italy: Report from 2016 survey on behalf of Artificial Network of Italian Society for Gastroenterology, Hepatology and Nutrition (SIGENP). *Nutrients* 2018; **10**:1311; https://doi:10.3390/nu10091311.
4. Fredriksson F, Nystrom N, Waldenvik K, *et al.* Improved outcomes of intestinal failure in preterm infants. *J Pediatr Gastroenterol Nutr* 2020: doi:10.1097/MPG.0000000000002763.
5. Brown SK, Davies N, Smyth E, *et al.* Intestinal failure: the evolving demographic and patient outcomes on home parenteral nutrition. *Acta Paediatr* 2018: **107**:2207-2211.
6. Hukkinen M, Merras-Salmio L, Pakarinen MP. Health-related quality of life and neurodevelopmental outcomes among children with intestinal failure. *Semin Pediatr Surg* 2018;**27**:273-279.
7. Norsa L, Artru S, Lambe C, et al. Long term outcomes of intestinal rehabilitation in children with neonatal very short bowel syndrome: Parenteral nutrition or intestinal transplantation. *Clin Nutr* 2019; **38**: 926-933.
8. Jo SY, McCallum Z, Shalley H, et al. Outcomes of children with chronic intestinal failure: Experience over 2 decades at a tertiary paediatric hospital. *J Pediatr Gastro Nutr* 2019; **69** (3): e79-e87.
9. Pironi L, Arends J, Baxter J, et al. ESPEN endorsed recommendations. Definition and classification of intestinal failure in adults*. Clin Nutr* 2015;**34**:171-80..
10. Wales PW, Christison-Lagay ER. Short bowel syndrome: epidemiology and etiology. *Semin Pediatr Surg.* 2010; **19**(1): 3-9.
11. Wales PW, de Silva N, Kim J, Lecce L, To T, Moore A. Neonatal short bowel syndrome: population-based estimates of incidence and mortality rates. Journal of pediatric surgery. 2004; **39**:690-695.
12. Glover JJ, Caniano DA, Balint J. Ethical challenges in the care of infants with intestinal failure and lifelong parenteral nutrition. *Semin Pediatr Surg.* 2001; **10(**4): 230-6.
13. Avitzur Y, Wang JY, de Silva NT, *et al*. Impact of Intestinal Rehabilitation Program and Its Innovative Therapies on the Outcome of Intestinal Transplant Candidates. *J Pediatr Gastroenterol Nutr.* 2015; **61**:18-23.
14. Stanger JD, Oliveira C, Blackmore C, Avitzur Y, Wales PW. The impact of multi-disciplinary intestinal rehabilitation programs on the outcome of pediatric patients with intestinal failure: a systematic review and meta-analysis. *J Pediatr Surg*. 2013; **48**:983-92.

15. Belza C, Wales PW. Impact of multidisciplinary teams for management of intestinal failure in children. *Curr Opin Pediatr* 2017; **29**:334-339.
16. Nader EA, Lambe C, Talbotec C, *et al*. Outcome of home parenteral nutrition in 251 children over a 14 y period: report of a single center. Am J Clin Nutr 2016; **103**:1327-1336.
17. Szlagatys-Sidorkiewicz, A. Borkowska A, Janowska A, *et al*. Reorganization of nutritional therapy can markedly reduce the rate of catheter-related blood stream infections in pediatric patients receiving parenteral nutrition - a 7-year prospective follow-up study. *Nutr Hosp*. 2014; **31**(3): 1116-1121.
18. Groen, H. Neelis EG, Poley MJ, et al. Intestinal rehabilitation for children with intestinal failure is cost-effective: a simulation study."*Am J Clin Nutr* 2017; **105**(2): 417-425.
19. Zemrani B, McCallum Z, Bines JE. Trace Elemant provision in parenteral nutrition in children; one size does not fit all. *Nutrients* 2018; **10**: doi:10.3390/nu10111819.
20. Colomb, V, Jobert-Giraud A, Lacaille F, Goulet O, Fournet JC, Ricour C. Role of lipid emulsions in cholestasis associated with long-term parenteral nutrition in children.2000; *JPEN J Parenter Enteral Nutr* **24**(6): 345-350.
21. Muhammed R, Bremner R, Protheroe S, Johnson T, Holden C, Murphy MS. Resolution of parenteral nutrition-associated jaundice on changing from a soybean oil emulsion to a complex mixed-lipid emulsion. *J Pediatr Gastroenterol Nutr* 2012; **54**(6): 797-802.
22. Goulet O, Antebi H, Wolf C, *et al*. A new intravenous fat emulsion containing soybean oil, medium-chain triglycerides, olive oil, and fish oil: a single-center, double-blind randomized study on efficacy and safety in pediatric patients receiving home parenteral nutrition. *JPEN J Parenter Enteral Nutr* 2010; **34**:485-95.
23. Diamond IR, Grant RC, Pencharz PB, *et al.* Preventing the Progression of Intestinal Failure-Associated Liver Disease in Infants Using a Composite Lipid Emulsion: A Pilot Randomized Controlled Trial of SMOFlipid. *JPEN J Parenter Enteral Nutr*. 2009; **41**:866-877.
24. Calkins KL, Dunn JC, Shew SB, Reyen L, Farmer DG, Devaskar SU, Venick RS. Pediatric intestinal failure-associated liver disease is reversed with 6 months of intravenous fish oil. *JPEN J Parenter Enteral Nutr* 2014; **38**:682-92.
25. Premkumar MH, Carter BA, Hawthorne KM, King K, Abrams SA. High rates of resolution of cholestasis in parenteral nutrition-associated liver disease with fish oil-based lipid emulsion monotherapy. *J Pediatr*. 2013; **162**:793-798 e1.
26. Wang C, Venick RS, Shew SB, Dunn JCY, Reyen L, Gou R, Calkins KL. Long-Term Outcomes in Children With Intestinal Failure-Associated Liver Disease Treated With 6 Months of Intravenous Fish Oil Followed by Resumption of Intravenous Soybean Oil. *JPEN J Parenter Enteral Nutr* 2019;**43**:708-716.
27. Ong ML, Venick RS, Shew SB, Dunn JCY, Reyen L, Grogan T, Calkins KL. Intravenous Fish Oil and Serum Fatty Acid Profiles in Pediatric Patients With

Intestinal Failure-Associated Liver Disease. *JPEN J Parenter Enteral Nutr* 2019; **43:**717-725.
28. de Meijer VE, Le HD, Meisel JA, Gura KM, Puder M. Parenteral fish oil as monotherapy prevents essential fatty acid deficiency in parenteral nutrition dependent patients. *J Pediatr Gastroenterol Nutr* 2010; **50:** 212-218.
29. Lapillonne A, Fidler Mis N, Goulet O, van den Akker CHP, Wu J, Koletzko B. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Lipids. *Clin Nutr* 2018;**37**:2324-2336.
30. Oliveira C, de Silva NT, Stanojevic S*, et al*. Clinical outcomes in pediatric intestinal failure: use of time-series analysis to assess the evolution of an intestinal failure program. *J Am Coll Surg*. 2016; **222**:1180-1188.
31. Lambe C, Poisson C, Talbotec C, Goulet O. Strategies to reduce catheter-related bloodstream infections in pediatric patients receiving home parenteral nutrition: the efficacy of taurolidine-citrate prophylactic-locking. *JPEN J Parenter Enteral Nutr* 2018; **42**:1017-1025.
32. Kawano T, Kaji T, Onishi S, *et al*. Efficacy of ethanol locks to reduce the incidence of catheter-related bloodstream infections for home parenteral nutrition pediatric patients: comparison of therapeutic treatment with prophylactic treatment*. Pediatr Surg Int* 2016; **32**:863-867.
33. Vegting IL, Tabbers MM, Benninga MA, *et al*. Prophylactic anticoagulation decreases catheter-related thrombosis and occlusion in children with home parenteral nutrition. *JPEN J Parenter Enteral Nutr* 2012; **36:**456-462.
34. Tappenden K. Intestinal adaptation following resection. *JPEN J Parenter Enteral Nutr* 2018; **38**:23S-31S.
35. Belza C, Betts Z, de Silva N, Avitzur Y, Wales PW. Factors related to the development of small-bowel bacterial overgrowth in pediatric intestinal failure: a retrospective cohort study. *JPEN J Parenter Enteral Nutr* 2020: doi:10.1002/jpen.1809.
36. Cole CR, Ziegler TR. Small bowel bacterial overgrowth: a negative factor in gut adaptation in pediatric SBS. *Curr Gastroenterol Rep*. 2007; **9**:456-462.
37. McGrath K, Pitt J, Bines JE. Small bowel bacterial overgrowth in children with intestinal failure on home parenteral nutrition. *JGH Open*. 2019: **3**:394-399.
38. Lauro A, Coletta R, Morabito A. Restoring gut physiology in short bowel patietns: from bench to clinical application of autologous intestinal reconstructive procedures. *Exp Rev Gastroenterol Hepatol*. 2019; **13**: 785-796.
39. Fitzgerald K, Muto M, Belza C, de Silva N, Avitzur Y, Wales PW. The evolution of the serial transverse enteroplast for pediatric short bowel syndrome at a single institution. *J Pediatr Surg* 2019; **54**:993-998.
40. Szkudlarek J, Jeppesen PB, Mortensen PB. Effect of high dose growth hormone with glutamine and no change in diet on intestinal absorption in short bowel patients: a randomized, double blind, crossover, placebo controlled study. *Gut* 2000; **47**:199-205.

41. Jeppesen PB, Pertkiewicz M, Messing B, *et al.* Teduglutide reduces need for parenteral support among patients with short bowel syndrome with intestinal failure. *Gastroenterology* 2012;**143**:1473-1481. e3.
42. Iyer KR, Kunecki M, Boullata JI, *et al.* Independence From Parenteral Nutrition and Intravenous Fluid Support During Treatment With Teduglutide Among Patients With Intestinal Failure Associated With Short Bowel Syndrome. *JPEN J Parenter Enteral Nutr* 2017; **41**:946-951.
43. Carter BA, Cohran VC, Cole CR, *et al.* Outcomes from a 12-Week, Open-Label, Multicenter Clinical Trial of Teduglutide in Pediatric Short Bowel Syndrome. *J Pediatr* 2017;**181**:102-111. e5.
44. Kocoshis SA, Merritt RJ, Hill S, *et al*. Safety and Efficacy of Teduglutide in Pediatric Patients With Intestinal Failure due to Short Bowel Syndrome: A 24-Week, Phase III Study. *JPEN J Parenter Enteral Nutr* 2019; **44**:621-631.
45. Fullerton BS, Hong CR, Jaksic T. Longterm outcomes of pediatric intestinal failure. Semin Pediatr Surg. 2017; 26:328-335.
46. Neelis E, Rijen N, Sluimer J, *et al.* Bone health of children with intestinal failure measured by dual energy x-ray absorptiometry and digital x-ray radiogrammetry. *Clin Nutr* 2018; **37**:687-694.
47. Gold A, Danguecan A, Belza C, *et al*. Neurocognitive functioning in early school-age children with intestinal failure. *J Pediatr Gastronerolo Nutr* 2020; **70**:225-231.
48. Venick RS, Duggan E, Whatley J. Current status of pediatric intestinal transplantation in the United States. *Curr Opin Organ Transpl* 2020; **25**:201-207.
49. Burghardt KM, Wales PW, de Silva N, Stephens D, Yap J, Grant D, Avitzur Y. Pediatric intestinal transplant listing criteria - a call for a change in the new era of intestinal failure outcomes. *Am J Transplant* 2015;**15**:1674-81.
50. Kaufman SS, Avitzur Y, Beath SV, Ceulemans LJ, Gondolesi GE, Mazariegos GV, Pironi L. New Insights Into the Indications for Intestinal Transplantation: Consensus in the Year 2019. *Transplantation* 2019; **104**:937-946.

Table 1
Functional Classification of Intestinal Failure

	Characteristics	Level of care required
Type I	Relatively temporary Duration <1 month Result of illness or recovering from surgery	Acute care hospitals able to administer inpatient PN safely to children
Type II	Acute condition Managed with medical and/or surgical intervention Duration variable but can be months/year Majority may require long-term PN therapy	Acute care hospitals with experience in complex IF surgery and medical management and able to offer comprehensive IF management working in consultation with an expert IF centre
Type III	Chronic intestinal failure Often permanent PN dependency Home PN	Acute care hospital with specialised multidisciplinary team with expertise in the comprehensive management of patients with chronic IF. Strong links with an intestinal transplant programme

IF = Intestinal failure; PN = Parenteral nutrition

Table 2:
Underlying condition s associated with chronic intestinal failure in children

Pathophysiology	Cause	Underlying disease
Reduction in small intestinal length or mass	Short bowel syndrome due to	
	(i) Surgical resection	Necrotising enterocolitis Abdominal wall defects including Gastroschisis, Omphalocele Intestinal atresia/s Malrotation/Volvulus Trauma
	(ii) Congenital malformation	Congenital short bowel syndrome
Mechanical abnormality of the intestine	Intestinal fistula	Post-surgical complication Inflammatory or infective complication
	Obstruction	Intra-abdominal tumour Congenital Diaphragmatic hernia
Intestinal dysmotility	Chronic intestinal pseudo-obstruction	Unknown
	Congenital disorder involving intestinal neurones	Total or sub-total aganglionosis Hollow viscous myopathy Megacystis, microcolon, intestinal hyper-peristalsis syndrome
	Generalised neurological and metabolic disorders	Congenital: structural neural defects, severe neurodisability, mitochondrial disorders, congenital glycosolation defects Acquired: Injury, Post-neurosurgical
Extensive small intestinal mucosal disease	Congenital enteropathies	Tufting enteropathy Microvillus inclusion disease Other rare conditions: including Tetratricopeptide repeat domain 7A

	Severe inflammatory or post-inflammatory intestinal injury	deficiency, Tricohepaticentric syndrome, Diacylglycerol-acyltransferase 1 deficiency Severe crohns disease Severe combined immune deficiency (SCID) Immune-mediated polyendocrinopathy X-linked syndrome (IPEX) Graft versus host disease Oncological disease/treatment

Table 3

Members of the Paediatric Intestinal Failure and Rehabilitation Multidisciplinary Team

Professional Group	Role
Paediatric Gastroenterologist	Inpatient and outpatient medical management, assessment of gastrointestinal function and absorptive status including endoscopy
Paediatric Surgeon	Gastrointestinal surgery, stomal care, central venous catheter placement, inpatient and outpatient surgical management
General Paediatrician	Inpatient and outpatient general paediatric care; specific behavioural and learning needs
Neonatologist	Care of the critically ill newborn
Interventional radiologist	Central venous line access and care
Nurse Specialist	Co-ordination of patient care, central venous access device management, Ostomy care, education and training for home care including parenteral and enteral nutrition, support for home PN
Dietitian	Monitoring of nutritional status, oversight of nutritional intake vs requirements, dietary advice, drug-nutrient interactions, management of enteral nutrition (formulae, equipment etc)
Pharmacist	Parenteral nutrition prescribing advice, manufacture and dispensing of PN, dispensing other drugs, drug-nutrient interactions
Social Worker	Social and emotional support to patient and the family, access to social benefits including NDIS, family support packages, emergency housing, carers and respite for families
Speech Therapist	Oral stimulation and support for early feeding, support for introduction of oral feeding in patients with oral aversion
Physiotherapist	Stimulation and mobilisation, particularly with prolonged hospitalisation or in association with other disabilities.
Mental Health professional	Behavioural and individual and family support strategies
Ward Unit Manager	Coordinate inpatient admissions and inpatient training

Table 4

Intestinal Failure Management

Strategy	Aim	Management Approach
Provision of Safe and Effective Parenteral Nutrition	Optimise nutritional status	Age and condition appropriate PN to meet fluid, electrolyte macro- and micro-nutrient requirements Monitoring to adjust for changes in clinical status, weight, activity, growth Stimulation of oral feeding
	Limit PN complications	Balanced PN solutions Prevention of PN contamination Cycling PN Routine monitoring of all aspects of PN provision Stimulation of enterohepatic circulation (oral/enteral feeding) Awareness of potential for potential drug-PN interactions Lipid minimisation/use of alternative lipid source
	Limit complications related to central venous access	Training in meticulous line care Line placement by experienced personnel Line and equipment selection – size, site, type, connectors, lines, filters, pumps etc Site care – dressing types, changes Line locks – ethanol, Tauralock®, antimicrobial Anticoagulation Early identification and appropriate treatment of infection
	Maintain quality of life	Holistic supportive approach to patient and family care Adapting to changing needs of the growing child

		Parent and carer respite Aware and address social and financial challenges Availability of an experience team member to address patient and/or family concerns
Intestinal Rehabilitation	Enhance intestinal adaptive response	Intraluminal nutrition and specific nutrients: Glutamine, pectin, short and long chain fatty acids Intestinal secretions: Pancreatic and bile Trophic hormones: Glucagon-like peptide-2, epidermal growth factor, insulin-like growth factor-1, growth hormone, others
	Minimise factors that may negatively impact on adaptation	Autologous intestinal reconstruction surgery To improve dysmotility, reduce intestinal stasis Increase functional absorptive surface area Prokinetic agents To improve dysmotility, reduce intestinal stasis Anti-secretory agents Reduce fluid, electrolyte and intestinal hormone losses; gastric acid suppression Pre- and probiotics Address imbalance of the gut microbiome
Intestinal Transplantation	Restore enteral autonomy Cease PN Eliminate dependency on a central venous access device Reduced mortality in patients with life threatening complications of IF Improve quality of life	Isolated intestinal transplant Intestinal-liver transplant Gastro-small and large intestinal transplant +/- liver transplant Multivisceral transplant

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