Optimizing Care
for Children with
Intestinal Failure

THE GUT & BEYOND

Esther Neelis

Optimizing care for children with intestinal failure: the gut and beyond

Esther Gesine Neelis

The study described in Chapter 7 in this thesis was supported by Stichting Zeldzame Ziekten Fonds.

STICHTING ZELDZAME ZIEKTEN FONDS

The printing of this thesis has been financially supported by:

- COSMED Benelux BV
- Department of Pediatric Surgery, Erasmus Medical Center-Sophia Children's Hospital
- Erasmus MC University Medical Center Rotterdam
- Eurocept Homecare
- Fresenius Kabi Nederland B.V.
- Mediq Nederland B.V.
- Nederlandse Vereniging voor Gastroenterologie
- Nutricia Advanced Medical Nutrition
- Nutricia Early Life Nutrition

Cover design & layout: Optima Grafische Communicatie
ISBN: 978-94-6361-313-2

Optimizing Care for Children with Intestinal Failure:
the gut and beyond

Het optimaliseren van de zorg voor kinderen met darmfalen:
meer dan de darm alleen

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de rector magnificus

prof. dr. R.C.M.E. Engels

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
woensdag 30 oktober 2019 om 11:30 uur

door

Esther Gesine Neelis
geboren te Heerenveen

Erasmus University Rotterdam

PROMOTIECOMMISSIE

Promotoren:	Prof. dr. E.H.H.M. Rings Prof. dr. R.M.H. Wijnen
Overige leden:	Prof. dr. J.C. Escher Prof. dr. D. Tibboel Dr. M.M. Tabbers
Copromotor:	Dr. J.M. Hulst

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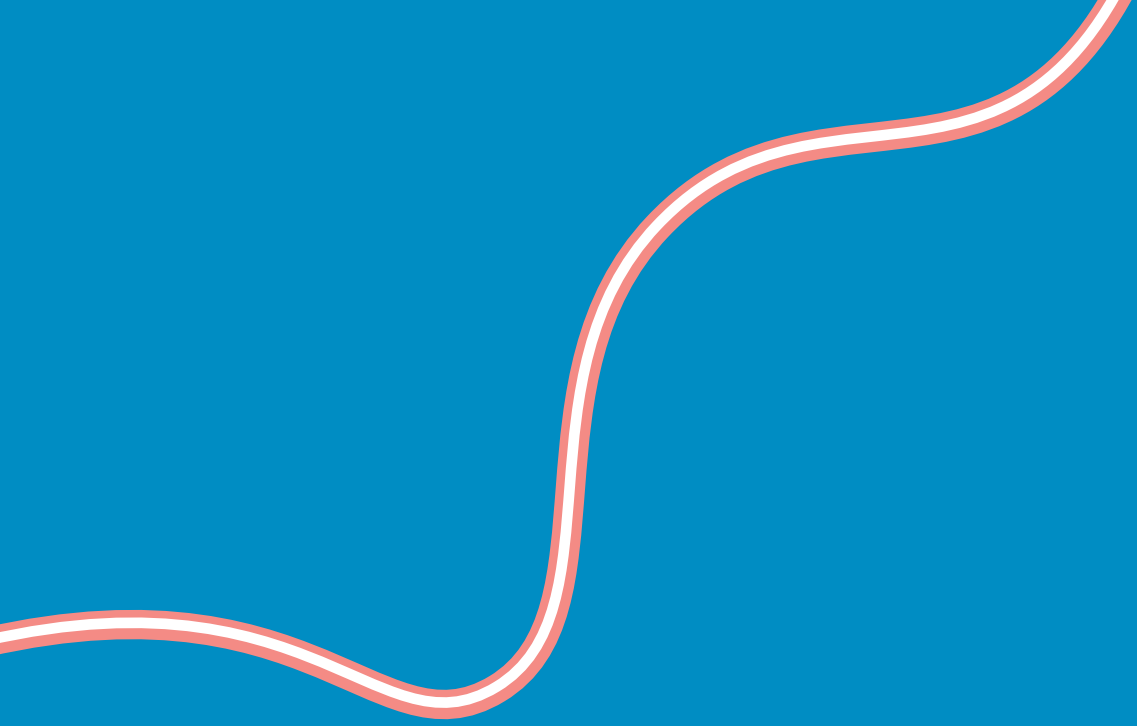

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General introduction

PROLOGUE

David was born at 36 weeks gestation. During pregnancy, doctors detected atresia of his small bowel. Surgery followed just after birth; the surgeon removed the obstructed parts as well as a distended part of 10 cm, leaving a small bowel length of 50 cm. David receives an ileostomy and is admitted to the intensive care unit. Because of the large part of his bowel that is missing, David cannot be fed normally. He depends on nutrition given directly into his vein via a central venous catheter, also known as parenteral nutrition. In the weeks after surgery, tube feeding is started and increased gradually. In the meantime, David's parents are busy trying to learn all the necessary medical procedures, such as how to take care of his ileostomy and how to administer the tube feeding and eventually parenteral nutrition.

After 4 months, David and his parents are finally able to go home. However, he is still dependent on parenteral nutrition, which is not without risks. Within 2 weeks after discharge, David is readmitted to the hospital because of a life-threatening line sepsis. In the years thereafter, he is often admitted because of many complications.

When David is 4 years old, he is going to school. Due to his central venous catheter and the fact that he is smaller than all of his classmates, David is different from other children. Most importantly, David is not able to simply have dinner together with his family or eat his favorite meal at his birthday. He is still receiving tube feeding and parenteral nutrition, and it is expected that he will need this for the rest of his life. Every 2 months, he visits the hospital for monitoring of his growth and possible complications, and nutritional adjustments.

David's story is illustrative of the uncertain and unpredictable course of many children with intestinal failure. The portrait of David illustrates both the need and our motivation to focus on optimizing care for this vulnerable group of patients. Instead of merely focusing on survival, the focus should also be on outcome beyond survival. We aim to optimize the care of children with intestinal failure on the long term; the results of our research are partly described in this thesis.

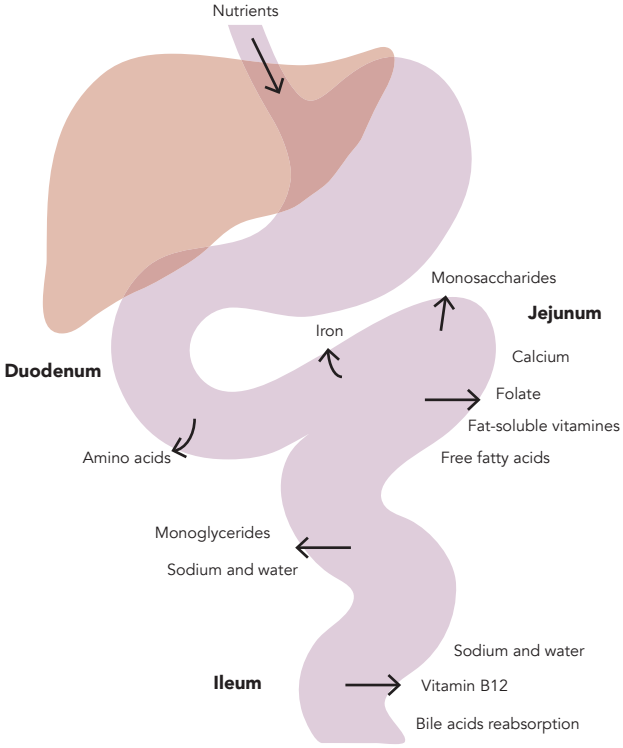
GENERAL INTRODUCTION

Intestinal failure

The intestine is known for two main functions: digestion and absorption of nutrients and fluids, and the maintenance of a barrier against the external environment. The combined length of the jejunum and ileum ranges from 3 to 8.5 m in adults.[1] The length of the large intestine or colon varies between 1 and 1.5 meters, and the colon is separated from the small intestine with the ileocecal valve. The small bowel is vital for motility, digestion and absorption of nutrients (**Figure 1**).

When the small bowel is too short or dysfunctional and not able to absorb enough nutrients, patients suffer from intestinal failure (IF).[2] This is a rare, though devastating disease, which results from obstruction, dysmotility, surgical resection, congenital defect, or disease-associated loss of absorption.[3] The main cause of IF in children is short bowel syndrome (SBS) after an extensive small bowel resection, accounting for at least 40% of the cases.[4-8] It often occurs in neonates for example due to necrotizing enterocolitis (**Figure 2**) or atresia of the small bowel (**Table 1**). Previous studies from Canada and the United States reported an incidence of neonatal SBS of 24.5 per 100.000 live births[8] and

Figure 1. Absorption of nutrients in the small bowel



an incidence of SBS between 0.7% and 1.1% depending on birth weight.[9] As the intestinal length in children is linked to gestational age and growth, it is difficult to define SBS in absolute terms.[10,11] A previous study measuring bowel length in children undergoing laparotomy showed that the small bowel length increased from a mean of 70 cm in those aged 24-26 weeks post-conception to 424 cm in those aged 49-60 months.[10] The Dutch National working group on SBS in children defined SBS as a resection of ≥ 70% of the small bowel and/or a remaining small bowel length (measured distal to the ligament of Treitz, i.e. jejunum and ileum) of < 50 cm in premature neonates, < 75 cm in term neonates and < 100 cm in infants above 1 year of age.[12] However, function of the small bowel is not dependent on length alone, and functional capacity of the intestine should also be taken into account. In clinical practice, children who only had a minor resection of the small bowel due to for example necrotizing enterocolitis or gastroschisis may also suffer from IF. These children do not fulfill the criteria for SBS, but the small bowel was probably more damaged than what was apparent during surgery. Next to surgical IF, other causes of IF are motility disorders and intrinsic disorders of the epithelium (enteropathies), including more rare diseases such as chronic intestinal pseudo-obstruction (Table 1). The clinical picture of IF is characterized by intolerance to enteral nutrition, leading to symptoms of diarrhea or high output stoma, abdominal pain, vomiting, dehydration and malnutrition.

Figure 2. Example of a child with necrotizing enterocolitis, a major cause of intestinal failure in neonates

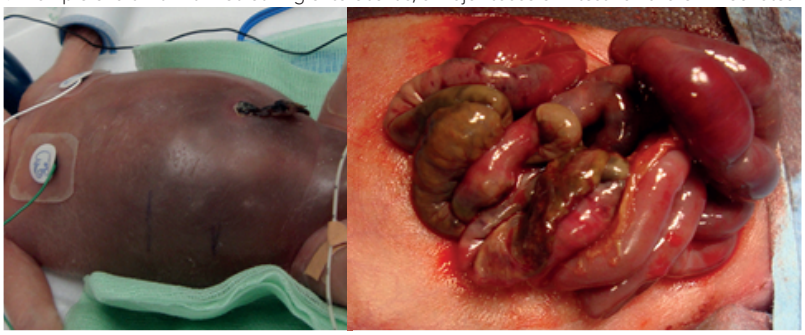


Table 1. Conditions leading to intestinal failure in children. Adapted from[2,13,14]

Surgical intestinal failure			**Functional intestinal failure**	
Prenatal	*Neonatal*	*Postnatal*	*Motility disorders*	*Enteropathies*
Intestinal atresia	Necrotizing enterocolitis	Midgut volvulus	Chronic intestinal pseudo-obstruction	Microvillus inclusion disease
Gastroschisis	Midgut volvulus	Complicated surgery	Total aganglionosis with jejuno-ileal involvement	Tufting enteropathy
Apple peel syndrome		Strangulation/ herniation		Syndromic diarrhea/tricho-hepato-enteric syndrome
Midgut volvulus				Autoimmune enteropathy

Parenteral nutrition

Since patients with IF cannot absorb enough nutrients and/or fluids via the intestine, they depend on parenteral nutrition (PN) to survive. Parenteral nutrition is a nutritional formulation that is administered intravenously, containing all necessary macronutrients (amino acids, carbohydrates, lipids) and micronutrients (electrolytes, trace elements, vitamins). It was developed by Dudrick et al., as described in 1968.[15] Safe, long-term administration of PN to the infant was first described a few years later.[16] PN is formulated according to the child's individual needs and can be given as total or partial amount of the nutritional intake.

For long-term administration of PN, a subcutaneously tunneled central venous catheter (CVC) is placed into one of the large central veins, most often the jugular or subclavian vein. Previously, children with IF needed to stay in the hospital their entire lives. Nowadays PN can be given at home in case of chronic or irreversible IF as home PN (HPN). To administer the PN and take care of the CVC, parents receive training during 1-2 weeks in the hospital.

The number of children in the United Kingdom receiving PN for 28 days or more has been estimated at 1300 per year.[17] HPN is rare, with a reported European prevalence in children ranging from 0.34 to 8.92 per million[18] and a more recent prevalence of 13.7 children per million in the United Kingdom[5] and 14.1 per million inhabitants in Italy.[19] The last registration of patients with chronic IF in the Netherlands took place in 2004, with a prevalence of 0.6 per million children.[20]

Intestinal adaptation

An important key to improved clinical outcome after extensive small bowel resection is the ability of the residual bowel to adapt, which is called intestinal adaptation. This natural compensatory process can take several months to years.[21,22] In animal studies, various structural and functional changes during adaptation have been described. The remaining mucosa becomes hyperplastic and muscular hypertrophy occurs. Crypt depth and villus height increase due to rapid cell proliferation and thereby increase the absorption capacity of the intestine.[23] Also angiogenesis, increased expression and activity of nutrient transporters and slowed intestinal transit are playing a role.[24] It is, however, not yet fully resolved whether all of these mechanisms contribute to intestinal adaptation in humans.[24]

The most important factor in stimulating intestinal adaptation is enteral nutrition (EN), which should be started as soon as possible. Stimuli from luminal content increase the release of trophic hormones and a number of nutrients have a direct trophic effect on enterocytes.[25-29] Additionally, EN stimulates normal biliary dynamics and improvement of bile flow, thereby reducing cholestasis.[30]

During the process of intestinal adaptation, the EN is gradually increased while the PN is decreased. Finally, the intestine may achieve partial or complete enteral autonomy, which allows patients to wean off PN. In current clinical practice, the process of increasing EN and decreasing PN is a matter of trial and error because there is no established marker available. As a consequence, EN might be increased too fast, resulting in excessive diarrhea and vomiting, or too slow – thereby increasing the risk of PN associated complications. Previously, some markers of intestinal adaptation have been assessed, of which citrulline is the most studied. Citrulline is a non-protein amino acid mainly synthesized from glutamine in the liver and small bowel. Previous studies demonstrated that plasma citrulline levels correlate with enterocyte mass in children with SBS[31] and that citrulline was a positive predictor of enteral autonomy.[32,33] The level of citrulline associated with weaning off PN varies among several studies, but is typically > 15-19 micromol/L.[34,35] However, most of these studies were cross-sectional and had a small sample size, and citrulline is currently not used in clinical practice. A marker of intestinal adaption would be of great help to evaluate intestinal adaptation and response to therapeutic interventions aimed at promoting adaptation, as well as allowing for earlier discrimination between patients who are able to wean off PN and those who will not achieve enteral autonomy.

Intestinal rehabilitation aims to maximize the response to intestinal adaptation through medical and surgical interventions that lead to enteral autonomy. The ability to achieve partial or complete enteral autonomy depends on a number of factors. In previous studies the remaining small bowel length has been found the most important factor in achieving enteral autonomy.[7,32,33,36-45] Other factors include (gestational) age, presence of ileocecal valve[7,36-38,41,43,44], presence of colon/colonic continuity[32,41,46] and the underlying disease itself. For instance, necrotizing enterocolitis has been associated with achieving enteral autonomy.[32,33,36,38] As expected, patients with SBS were more likely to wean off PN compared to patients with motility disorders or enteropathies.[33,44,45] The number of patients able to wean off PN differs among studies, mostly varying between 40 and 70%.[32,33,36-38,40,47,48] Yet, comparison of the data is limited or difficult because of the variety in patient populations included, criteria to define IF and different durations of follow-up. A previous study using time series analysis showed that the introduction of an intestinal rehabilitation program, the serial transverse enteroplasty intestinal lengthening procedure, omega-3 lipid emulsions and ethanol locks did not change parenteral nutrition weaning.[49]

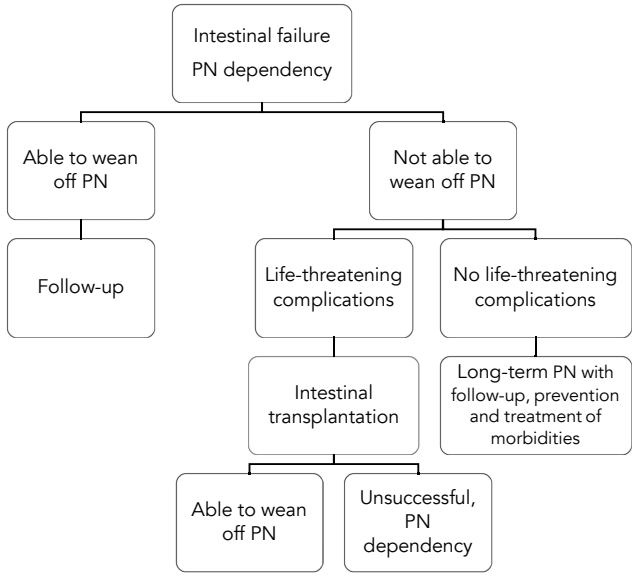
Surgical management of intestinal failure

Standard general surgical interventions in the management of IF include formation and closure of ostomies and fistulas. Other surgical techniques comprise intestinal lengthening procedures and intestinal transplantation (ITx). As part of intestinal adaptation, the intestine may dilate. In 1980, Bianchi first described a longitudinal intestinal lengthening

procedure (known as the Bianchi procedure).[50] Another intestinal lengthening procedure is the serial transverse enteroplasty procedure (STEP).[51] With both procedures the goal is to decrease the bowel diameter to normal and lengthen the small bowel. A recent systematic review concluded that 87% of children who underwent STEP had an increase in enteral tolerance[52], although weaning off PN often remains impossible after STEP. In addition, re-dilation is common for both procedures.[53]

Intestinal transplantation (ITx) is reserved as a treatment option for patients with IF with life-threatening complications or when HPN fails (**Figure 3**), although in the Netherlands there is a cautious-restrictive policy because of the better survival on HPN compared to survival after ITx. The most recent report of the Intestine Transplant Registry reveals patient survival rates (combined for adults and children) of 77%, 58% and 47% at 1, 5 and 10 years, respectively, after transplant for patients transplanted after 2000, while graft survival was 71%, 50% and 41%, respectively.[54] Current indications are life-threatening sepsis, impending loss of central venous access, extreme SBS, congenital mucosal disorders, end-stage liver disease and IF with high morbidity and poor quality of life[55]. However, given the increasing ability to successful intestinal rehabilitation, some speculate that the criteria need to be reviewed.[56]

Figure 3. Algorithm for intestinal failure management

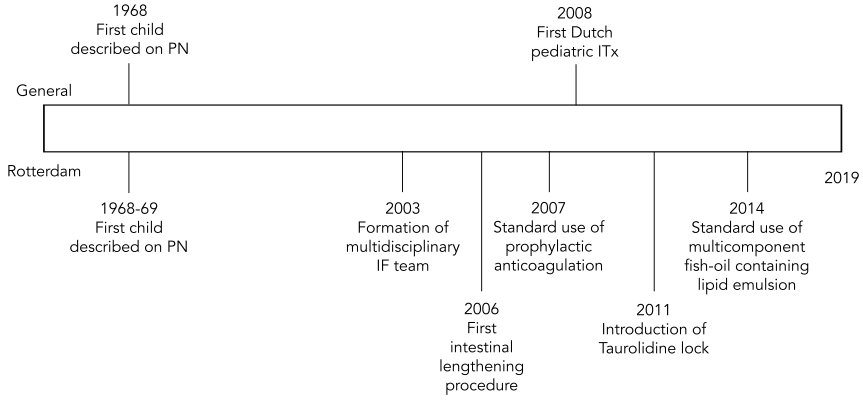


Abbreviation: PN, parenteral nutrition.

Prognosis

Until 15 years ago, the prognosis of IF was poor, especially in the neonatal period. Over the last decades, HPN has increased rapidly due to the improvement in survival with better quality of surgical treatment, neonatal care, and advancements in the treatment of IF such as the availability of catheter lock solutions to prevent CVC-related blood stream infections and the development of new parental lipid emulsions containing fish-oil (**Figure 4**).[5] Yet the mortality of underlying diseases such as necrotizing enterocolitis is still high, and it should be kept in mind that these patients who die before even going home on HPN, are not taken into account in studies regarding the mortality of IF.

Figure 4. Timeline showing introduction of new treatment strategies for intestinal failure patients in the Erasmus MC – Sophia Children's Hospital, Rotterdam, the Netherlands



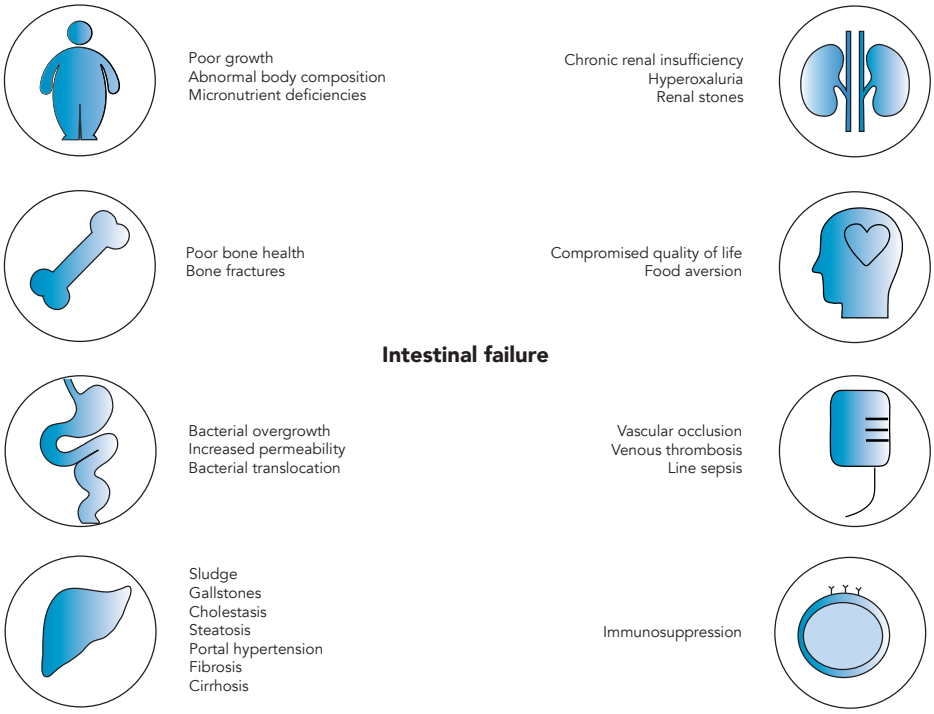
Abbreviations: IF, intestinal failure; ITx, intestinal transplantation; PN, parenteral nutrition.

Previous research from the largest center for HPN in children from France established that the survival probability at 5 years was 89%, and at 10 years 81%.[7,57] The likelihood and cause of death also depend on the underlying disease. Factors associated with greater mortality are start of PN at an early age, particularly in the neonatal period, having primary non-digestive disease and necrotizing enterocolitis.[7,58-60] In general, congenital mucosal disease has a higher mortality rate than SBS, whereas chronic intestinal pseudo-obstruction has a lower mortality rate than SBS.[57,58]

Morbidities related to intestinal failure

The improved survival has made the long-term outcomes and quality of life of patients with IF increasingly important. PN is still associated with frequent and potentially life-threatening complications (**Figure 5**). Because of advancements in the treatment of IF, complications such as line sepsis and liver failure are (expected to be) less common than before, and long-term morbidities such as growth failure, poor bone health and abnormal body composition deserve more attention.

Figure 5. Overview of complications of intestinal failure



Growth failure and abnormal body composition

Current growth monitoring and estimation of nutritional requirements is based on the measurement of weight and length/height. Many children with IF show poor growth, being shorter and lighter than healthy references.[61,62] Quality of growth, i.e. body composition (fat mass and fat free mass), is not measured routinely in clinical practice. Body mass index is often used as a proxy of body composition, although it was shown that this marker is not accurate in estimating obesity in children.[49] Other methods to measure body composition include dual energy X-ray absorptiometry (DEXA), double-labelled water, bio-impedance and air displacement plethysmography. One previous study using DEXA to investigate the body composition in children with IF aged > 5 years showed that children with IF have a lower fat free mass and that fully PN-dependent children had increased fat mass.[63]

Adequate growth and nutritional intake are important, as malnutrition in infancy has been associated with adverse long-term outcomes such as impaired neurodevelopment in otherwise healthy children.[59,64] Abnormal body composition is associated with determinants of cardiovascular disease, type 2 diabetes mellitus and metabolic syndrome.[65] In addition, fat free mass is essential for developing bone mass.[66,67]

Currently it is not well known how long-term growth is characterized in IF-patients treated in the Erasmus MC-Sophia Children's Hospital. Similarly, it is not well known how the course of growth is after weaning off PN. Additionally, the body composition of patients with IF has not been investigated widely, especially not in infants.

Poor bone health

Poor bone health is multifactorial and may be caused by malabsorption of nutrients such as calcium and vitamin D, possible side effects of medication, chronic intestinal inflammation, lack of physical activity (i.e. weight-bearing exercise), the use of PN and the underlying disease itself. Children with IF have a lower bone mineral density (BMD) than healthy controls. The prevalence of low BMD varies between 12.5% and 83%.[61,68,69] The main limitations of the available studies investigating bone health are the lack of follow-up data and the small sample sizes. Current monitoring of bone health takes place from the age of 4-5 years onwards, when reference data are available for DEXA, the golden standard to assess bone health. Since it is not well known how to monitor bone health in patients below the age of 4-5 years, bone health of infants with IF has not been investigated yet.

Altered gut microbiome

Several factors in patients with IF predispose to small intestinal bacterial overgrowth (SIBO), defined as > 10^5 colony forming unites per mL of bacteria in the proximal small bowel.[16] Several factors intrinsic to IF predispose to bacterial overgrowth such as the absence of the ileocecal valve and a disturbed motility. SIBO in children is often clinically diagnosed, based on symptoms such as bloating, abdominal distension, flatulence, abdominal discomfort and diarrhea, which are often difficult to distinguish from symptoms directly caused by IF. It is empirically treated with antibiotics. Knowledge of the bacteria that are overabundant may help in a more targeted approach with antibiotics or for example probiotics. Several, mostly cross-sectional studies were published investigating the microbiome in children with IF, showing that the overall bacterial diversity is decreased.[70-72] In addition, a shift from Gram-positive bacteria to Gram-negative Proteobacteria was found[71-74], as well as an overabundance of Lactobacillus.[71,72,74] Nevertheless, most of these studies lack details on important clinical factors such as enteral/oral nutrition and use of antibiotics. Additionally, the metabolic activity of the microbiome is not well known.

Psychosocial morbidity and quality of life

Intestinal failure can have profound psychosocial consequences for the patients and their families. Results of previous studies are conflicting: in some studies children and their parents reported a decreased health-related quality of life compared with healthy

children[75,76] and were psychologically distressed[77], while in other studies the long-term quality of life was comparable with that of healthy peers.[78,79] A qualitative study showed that children coped well with the PN, but are burdened by the complications of the therapy and the underlying disease.[80] Children with IF have obvious symptoms that may impact their quality of life, such as diarrhea and vomiting. Moreover, the inability to eat orally may have a great impact. These items are often not part of the quality of life questionnaires in the performed studies.

Next to the effects on the quality of life of the child, the burden of care on parents is enormous. The fact that the child suffers from IF might lead to parental stress and concerns about their child's current and future health, but also financial concerns may play a role. A previous study showed that parents experience a lower quality of life, reporting problems in social life and family life.[81] There is a lack of information regarding the effects of having a child with IF on the family.

Organization of care

In the Netherlands, HPN for children is offered and coordinated by specialized centers. Currently, the two largest centers are in Amsterdam (Academic Medical Center-Emma Children's Hospital, currently Amsterdam UMC, Emma Children's Hospital) and Rotterdam (Erasmus Medical Center-Sophia Children's Hospital). HPN for children is also provided in Nijmegen (Radboud University Medical Center Nijmegen-Amalia Children's Hospital) and some children with IF are also seen in Groningen (University Medical Center Groningen-Beatrix Children's Hospital), in close collaboration with Amsterdam for the production and delivery of PN. Intestinal transplantation is performed in the University Medical Center Groningen.

Setting up multidisciplinary teams or intestinal rehabilitation programs is one of the most important measures that could improve the outcome of children with IF. A European study showed that the risk of death is increased by absence of such a team.[60] In the same way, implementation of these teams reduced the number of septic episodes and improved survival.[49,82] In Rotterdam, a multidisciplinary team treats children with IF; this team includes pediatric gastroenterologists, pediatric surgeons, dietitians and specialized nurses. After an often long hospital admission, children discharged on HPN are frequently seen by this multidisciplinary team at the outpatient clinic, with the frequency depending on their age and clinical condition. Care of patients with IF is complex, and requires prolonged and frequent hospital admissions, multiple surgical procedures, frequent outpatient visits and specialized nutritional support. From a health economic perspective, the health care burden of IF is enormous. Yet, studies regarding costs are scarce and have mainly focused on SBS.[83]

The most common guideline used for HPN in children is the general guideline on PN from the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), including one chapter on HPN in which up-to-date details of treatment are lacking.[4] In addition, current clinical practice is not well known and may differ among specific centers and countries.

Conclusion

In conclusion, the treatment of children with IF has mainly focused on survival. Advancements in the care for children with IF have led to a better prognosis on HPN. However, many long-term effects of IF and PN are currently not well known, including optimal growth, body composition and bone health. Additionally, organizational aspects including the current organization and clinical practice of pediatric IF teams, as well as the costs of IF are not well known.

AIMS AND OUTLINE OF THIS THESIS

A better understanding of the complications of IF would enable us to improve the care of children with IF. Therefore, the main aims of this thesis are to study the long-term outcomes of patients with IF and to evaluate organizational aspects important in the care of these patients.

Part I – Clinical aspects

In **Chapter 2** we provide an overview of aspects that are important in promoting intestinal adaptation, including nutrition and medication.

Chapter 3 describes the physical growth, body composition and prevalence of micronutrient deficiencies of patients with IF receiving HPN during PN and after weaning. **Chapter 4** assesses body composition using air displacement plethysmography in children receiving long-term PN and relates this to their growth. **Chapter 5** describes the results of a study in which the bone health of children with IF was evaluated. In addition, two methods to assess bone health were compared: dual energy X-ray absorptiometry and digital X-ray radiogrammetry.

Chapter 6 reviews what is known about the microbiome in patients with IF and how the microbiome could be used as a biomarker and therapeutic target in the future. In **Chapter 7** the microbiota and its metabolic activity of patients receiving long-term PN are described in a longitudinal way.

Chapter 8 focuses on the quality of life of parents with children with IF.

Part II – Organizational aspects

In **Chapter 9** the results are described of a multicenter registry of all patients with IF, both adults and children, in the Netherlands. **Chapter 10** reports the costs of treatment of children with IF, and evaluates the cost-effectiveness of intestinal rehabilitation. **Chapter 11** highlights the organization and clinical practice of IF teams across Europe by an international survey.

The last part of this thesis is dedicated to the general discussion and suggestions for future research in **Chapter 12**. A summary of the main findings of this thesis, in English and Dutch, can be found in **Chapter 13.**

The reported studies included patients treated and followed by the IF teams in the Erasmus MC-Sophia Children's Hospital in Rotterdam (chapters 3, 4, 5, 6, 8, 9 and 10), the Academic Medical Center in Amsterdam (chapters 4, 8, 9), the Radboud University Medical Center (chapter 9) and the University Medical Center Groningen (9 and 10).

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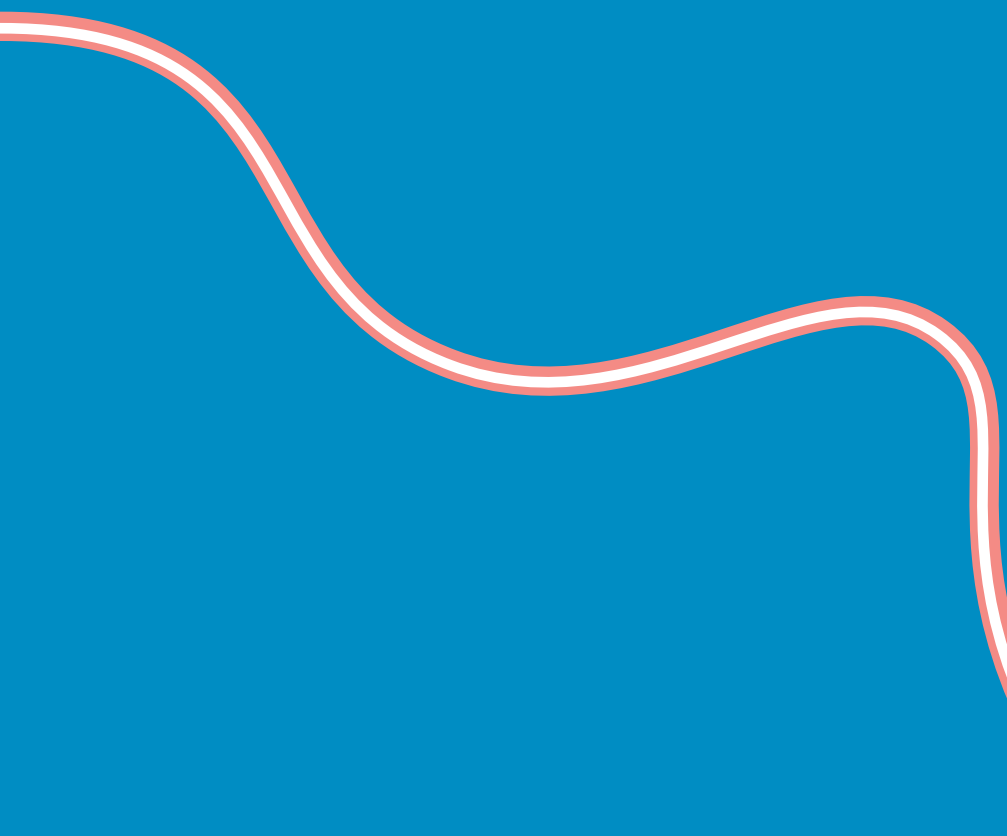
PART I

CLINICAL ASPECTS



2

Promoting intestinal adaptation by nutrition and medication

Best Pract Res Clin Gastroenterol. 2016 Apr;30(2):249-61.

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ABSTRACT

The ultimate goal in the treatment of short bowel syndrome is to wean patients off parenteral nutrition, by promoting intestinal adaptation. Intestinal adaptation is the natural compensatory process that occurs after small bowel resection. Stimulating the remaining bowel with enteral nutrition can enhance this process. Additionally, medication can be used to either reduce factors that complicate the adaptation process or to stimulate intestinal adaptation, such as antisecretory drugs and several growth factors. The aim of this review was to provide an overview of the best nutritional strategies and medication that best promote intestinal adaptation.

The main cause of intestinal failure (IF) in both adults and children is short bowel syndrome (SBS), which occurs after an extensive small bowel resection. Intestinal adaptation is the natural compensatory process that occurs after bowel resection. By effecting structural and functional changes this process improves nutrient and fluid absorption in the remnant small bowel.[1] Although not possible in all patients, the ultimate goal is to wean patients off parenteral nutrition (PN) by stimulating the intestinal adaptation, while ensuring adequate nutritional status and preventing complications. Many factors affect the process of adaptation, such as age of the patient, remaining small bowel length, presence of the ileocecal valve and colon and the underlying disease. Stimulating the remaining bowel with enteral nutrition (EN) can enhance adaptation. Additionally, medication can be used to either reduce factors that complicate the adaptation process or to stimulate intestinal adaptation, such as antisecretory drugs and growth factors. The aim of this review was to provide an overview about the nutritional strategies and medication that best promote intestinal adaptation.

This review is evidence-based wherever possible; meta-analysis data, systematic reviews and RCTs are described where available. However, in general, no large trials regarding nutrition and medication in patients with SBS have been performed and therefore also other studies and clinical practice guidelines are described.

NUTRITIONAL STRATEGIES

It is generally accepted that EN enhances intestinal adaptation in patients with SBS. The complex mechanism of action can be broken down into three major categories: 1) stimulation of mucosal hyperplasia by direct contact with epithelial cells; 2) stimulation of trophic gastrointestinal hormone secretion; and 3) stimulation of the production of trophic pancreatobiliary secretions.[2,3] In addition, it is known that the higher the complexity of a nutrient, the higher the workload of the digestive mechanisms involved. Thus, the more digestion a nutrient needs (e.g. whole protein), the more hyperplasia it will cause. In the next section, we will discuss what is known about the different nutrients in relation with intestinal adaptation in patients with SBS. In addition, the composition of EN and feeding mode will briefly be discussed.

Nutrients

Proteins

Dietary proteins are either digested into amino acids and directly absorbed, or digested into polypeptides, which are first absorbed inside the enterocytes before they are hydrolysed to amino acids.[4] Dietary protein hydrolysates have been developed to optimize both absorption pathways.[5] A study has shown that the peptide chain length of the hy-

drolysate affects the absorption of nitrogen and other amino acids residues; the nitrogen absorption rate from hydrolysates containing di- and tripeptides was higher than that from hydrolysates with longer peptide chain length (> pentapeptides).[6] In addition, a few other studies have shown found that protein hydrolysate solutions appeared to empty from the stomach faster than whole protein solutions and elicited a more rapid increase in plasma amino acid, glucagon and insulin concentrations in enterally fed surgical patients.[7,8] Whole protein is preferred in terms of optimizing intestinal adaptation. When whole protein is not tolerated, hydrolysates can be used.[9,10] Since it is hypothesized that whole protein optimizes intestinal adaptation, the use of hydrolysates is not recommended.

Carbohydrates

Studies on the effect of carbohydrates in patients with SBS reported conflicting results. In a descriptive case-series, adults with SBS and intact colon absorbed no more than 52% of 50 gram ingested carbohydrates, while 48% were fermented in the colon.[11] Another study found that adults with SBS and intact colon receiving a diet high in carbohydrates had significantly less faecal energy loss than those on a diet high in fat. This difference, however, was not observed in patients without a colon.[12]

This beneficial effect of a diet high in carbohydrates was not supported by other studies. For instance an RCT in adults showed that neither a high fat diet nor a high carbohydrate diet was beneficial to the overall absorption.[13] Another RCT demonstrated that a high fat diet did not influence the volume of jejunostomy output compared to a high carbohydrate diet.[14] In addition, experts suggest that a high load of carbohydrates (mainly monosaccharides and disaccharides) might cause diarrhoea.[15] They argue that restriction of the overall enteral carbohydrate load helps reduce the osmotic load and the substrate for bacterial overgrowth.[15] As far as we know, this theory is not supported by other studies. However, when bacterial overgrowth is present, a carbohydrate reduced diet is sometimes used.

A specific carbohydrate that deserves attention is lactose. Lactose intolerance may occur in after proximal jejunum resection. A cross-over study in adults with SBS demonstrated similar tolerance of a lactose-free diet and a diet containing 20 grams lactose a day.[16] Since there is not enough evidence, a lactose free diet is not recommended for routine use in patients with SBS.

Dietary fiber

Dietary fiber can be divided into soluble and insoluble forms. Insoluble forms (e.g. cellulose found in cereals) bind to water and cause bulking and softening of the stool, shortening the whole gut transit time. Soluble fiber (e.g. pectin, guar gum found in fruits

and vegetables) slow gastric emptying and the overall gut transit time, resulting in a mild anti-diarrheal effect.[17,18] Bacterial fermentation of soluble fiber in the colon produces short chain fatty acids (SCFAs), which account for 5-10% of the total energy intake.[19] A recent study showed that starch is the primary carbohydrate substrate for colonic bacterial fermentation in patients with SBS, although pectin also enhances SCFA production and fluid absorption.[20] Animal studies showed that pectin enhanced bowel adaptation.[21,22] Only one case study reported that pectin supplementation in a single patient caused a prolonged transit time and higher nitrogen absorption.[23] In clinical practice, dietary fiber supplementation is only recommended if the colon is present.[24]

Lipids

Long chain triglycerides (LCTs) undergo bile dependent hydrolysis within the enterocyte, before export into the lymphatic system as chylomicrons. It is thought that LCTs enhance bowel adaptation.[25] In response to the presence of LCTs, the secretion of PYY and glucagon-like peptide 2 is stimulated, which process mediate the ileal and jejunal brake phenomenon[26] resulting in slower transit time. LCTs contain n-3 long chain polyunsaturated fatty acids (LCPs), which might be useful in feeds for SBS patients, although more convincing data are needed.[5] They are known to have anti-inflammatory effects and were shown to improve the splanchnic circulation.[5] Two case-series reported that enteral n-3 LCPs might also improve cholestasis in infants with SBS.[27,28] In contrast, medium-chain triglycerides (MCTs) are absorbed directly across the enterocyte into the portal circulation. This starts in the stomach. An RCT in patients with jejuno- or ileostomy demonstrated that a diet containing high concentrations of MCTs can cause osmotic diarrhoea as a result of rapid hydrolysis of MCTs.[29] In contrast, MCTs improved fat absorption in patients with an intact colon and therefore might be beneficial for patients with bile acid or pancreatic insufficiency.[29] MCTs however do not contain essential fatty acids. In terms of optimizing intestinal adaptation, EN containing LCTs should be used.

Composition enteral nutrition

The composition of EN in patients with IF is much debated. It should take into account the patient's age, underlying diagnosis, length and type of the remaining small bowel and presence of the ileocecal valve and colon. Moreover, different overlapping goals, such as optimal stimulation of adaptation versus rapid weaning off PN, might influence the composition.

High quality RCTs on EN in adults and children are scarce, however, and most data are derived from outcomes of retrospective observational studies and/or case reports.[24]

Human milk

It has been postulated that human milk, which contains glutamine and other growth factors, enhances bowel adaptation.[5] A few cohort studies demonstrated that human milk contains high amounts of nucleotides, immunoglobulin A and leucocytes, which support the immune system of the neonate.[30] It is therefore hypothesised that the immunoglobulins and antimicrobial peptides of human milk enhance mucosal barrier function and prevent bacterial overgrowth.[31] Human milk also promotes intestinal colonisation with appropriate lactobacilli and related bacteria, which are important elements of the healthy microbiome.[32] Animal studies indicated that bovine colostrum is beneficial to bowel adaptation.[33] Two studies in humans, however, could not confirm this.[34,35] Another human study found that breastfed infants with SBS were weaned off PN earlier than non-breastfed SBS infants.[9] RCTs in infants are needed to elucidate the role of human milk on bowel adaptation and the possible advantages of human milk over formula feeding.

Polymeric, oligomeric or monomeric nutrition

Paediatric and adult studies report contradictive findings concerning the type of nutrition. An RCT in children found no difference in absorption between polymeric (containing whole protein, complex carbohydrates and LCT's) and oligomeric formulas (containing protein hydrolysates, complex carbohydrates and MCT's).[10] Small case series, however, found that a monomeric formula (containing amino acids, complex carbohydrates and LCT's) improved feeding tolerance.[36] In seven adults with a high jejunostomy no difference in absorption between polymeric and oligomeric formulas was found.[37] On the other hand, a small RCT in adults with high jejunostomy demonstrated that nitrogen absorption improved with an oligomeric diet.[38] In terms of promoting intestinal adaptation, human milk or a polymeric formula should be used, depending on the age of the patient.

Feeding mode

It is hypothesized that continuous administration of EN enhances enteral absorption by maximizing saturation of the carrier proteins and thereby increasing intestinal function. Case series in adults with SBS showed that when continuous EN was started early, enteral autonomy could be attained after only a mean of 36 days after surgery.[39] A study in children showed that continuous EN promoted nutrient retention and weight gain.[40] However in children with SBS, developing and preserving oral skills is always a priority.[5]

Conclusion

In conclusion, when aimed at promoting intestinal adaptation, EN should consist of complex nutrients i.e. whole proteins, complex carbohydrates and LCT's. However, on individual indication, such as the absence of specific parts of the bowel, adjustments in

the composition of EN might be necessary. While at least a part of EN should be given continuously, small amounts should be given orally to preserve oral skills.

PHARMACOLOGIC TREATMENT

Medication used during the adaptation process can be divided into different subgroups based on their actions: antisecretory, antidiarrheal/antimotility, prokinetic, drugs to treat small intestinal bacterial overgrowth and growth factors (**Table 1**).[26,41,42]

Table 1. Medication used in the treatment of patients with SBS to reduce factors that complicate the adaptation or stimulate intestinal adaptation

Aetiology	Medication
Gastric acid hypersecretion	Histamine receptor antagonist (e.g. ranitidine)
	Proton pomp inhibitor (e.g. omeprazole)
	α2-Adrenergic receptor agonist (e.g. clonidine)
	Somatostatin analogue (e.g. octreotide)
Rapid intestinal transit	Antidiarrheal/antimotility agents (e.g. cholestyramine)
Intestinal dysmotility	Prokinetic agents (e.g. erythromycin)
Small intestinal bacterial overgrowth	Antibiotics (e.g. metronidazole)
	Probiotics (e.g. Lactobacillus rhamnosus (LGG))
Promoting intestinal adaptation	Growth factors (e.g. GLP-2 analogue teduglutide)

Antisecretory medication

A large fluid volume (up to 10 L) is produced and presented daily to the gastrointestinal tract. In healthy adults the small bowel absorbs all but 2 L of fluid, and the colon absorbs 90% of the remaining fluid volume. In patients with SBS fluid losses are a challenging problem. Agents that either inhibit active secretion or stimulate fluid absorption can tackle this problem and alleviate symptoms.

H2 receptor antagonist & Proton pomp inhibitors

After a large small bowel resection, hypergastrinemia occurs which in turn leads to transient gastric hypersecretion that can last up to one year.[43] This is most likely due to inadequate gastrin catabolism in the gut lumen or to decreased secretion of inhibitory hormones. H2 blockers (e.g. ranitidine, famotidine, and cimetidine) inhibit histamine at the histamine H2 receptors of the gastric parietal cells, thus reducing gastric acid secretion, whereas PPIs (such as omeprazole and esomeprazole) stop acid secretion by directly inhibiting the H+/K+-ATPase pump of parietal cells.

For infants with SBS, no safety or efficacy studies on the use of PPIs have been performed. In one case report on a child with SBS[44], ranitidine was found effective in suppressing gastric acid hypersecretion. Omeprazole significantly reduced stool output and sodium losses in adult patients more than 6 months after bowel resection, whereas ranitidine had no effect.[45,46]

For clinical practice, H2 blockers and PPIs can be useful early after bowel resection. H2 antagonists, which have less efficacy than PPIs, are generally considered second-line treatment.

Clonidine

Clonidine is an alpha-2 adrenergic receptor agonist that has both a central and peripheral mechanism of action, reducing small and large bowel motility and prolonging gastric emptying and intestinal transit times. Clonidine also decreases bicarbonate secretion and increases sodium absorption, which promotes passive water diffusion across the enterocyte and diminishes intestinal fluid losses.[47-49] Only few studies of clonidine use in patients with SBS have been performed; none specifically in children. These studies showed a longer intestinal transit time and decreased faecal weight loss and faecal sodium loss.[47,48,50] Given the potential for adverse effects and the likelihood of limited reductions in output, this medication should be restricted to SBS patients with high-output jejunostomies who cannot be controlled otherwise.

Somatostatin analogue

Octreotide is the long-acting analogue of somatostatin that is primarily produced by the pancreas and along the gastrointestinal tract and inhibits secretion of multiple enteric hormones like CCK, gastrin and motilin.[51] Octreotide has been used in SBS to reduce gastric hypersecretion, salt and water secretion and prolong gastrointestinal transit time.[52] In two infants with IF, stool output and PN dependency improved, although side-effects occurred.[53] Octreotide reduced stoma output by an average of 3.3 L/day in 10 adult patients with end-jejunostomy dependent on PN.[54] It is not considered a first-line drug because of the inconvenience of subcutaneous injection, high costs and side effects.[55,56] Octreotide may benefit those patients with severe diarrhoea insensitive to other medical alternatives.

Antidiarrheal/antimotility medication

Symptoms of SBS such as diarrhoea, dehydration and malabsorption are dependent on the degree and type of bowel segment resected. The ileum, in contrast to the jejunum, is more able to adapt to functional loss of the intestine. It absorbs bile acids and fluids, and slows small bowel motility via the ileal brake. Antidiarrheal/antimotility and antisecretory drugs are the first line therapy.[41] There is a great variability in the application of these

therapeutic strategies; however, none of the used agents is backed by scientific evidence in SBS patients.

Loperamide

Loperamide binds to the opioid receptor, thereby slowing the intestinal motility and increasing the transit time.[57] The faecal volume decreases with increase of consistency. The increased absorption results in depressed secretion of gastric fluid, bile acids and pancreatic enzymes.[58] Loperamide can normally be absorbed and taken up into the enterohepatic circulation, which is especially important after ileum resection.

Cholestyramine

Normally, a considerable proportion of the endogenous bile acid pool is regenerated by enterohepatic circulation in the terminal ileum. In patients with SBS in whom functional bile uptake is significantly reduced and intestinal continuity is re-established, the unabsorbed bile acids enter the colon, causing secretory diarrhoea. Bile acid-binding resins, such as cholestyramine, could alleviate these symptoms. On the other hand, more extensive ileal resections cause a net loss of bile acids because more bile acids are excreted than can be replaced through liver synthesis. For these patients, bile acid-binding drugs can exacerbate steatorrhea and fat malabsorption and should be avoided.[59]

Glucagon-like peptide 1 receptor agonist

In five adult patients suffering from SBS who received exenatide, a glucagon-like peptide 1 (GLP-1) receptor agonist, stool frequency and form improved and three of them patients could be weaned off PN.[60] Further research is necessary before exenatide can be used in clinical practice.

Prokinetics

When intestinal dysmotility of the gastrointestinal tract is present, prokinetic drugs can be prescribed. Erythromycin helps with gastric emptying, whereas domperidone increases gastric and duodenal motility. In addition, specialized IF teams often prescribe amoxicillin/clavulanic acid.[61] The evidence for these agents is heterogeneous, however, and scarce in patients with IF.[62] Usually, these agents are prescribed for a trial period and discontinued if no effect is observed.

Drugs to treat small intestinal bacterial overgrowth

Small intestinal bacterial overgrowth (SIBO) is a common problem in patients with IF. The following definition is most frequently used: microbiological presence of 10^5 or more colony forming units/ml of bacteria grown from a jejunal aspirate.[63] Risk factors are resections including removal of the terminal ileum and/or ileocecal valve, presence of

blind bowel loops, small bowel dilatation, strictures, dysmotility and specific underlying diseases such as chronic intestinal pseudo-obstruction. Furthermore, antisecretory and antimotility agents, as described above, can disturb the normal bacterial flora. Symptoms of SIBO include diarrhoea, abdominal pain, abdominal distension, steatorrhea, cramping, flatulence and weight loss.[64] Besides, SIBO may lead to impaired absorption of nutrients, resulting from maldigestion in the lumen or malabsorption due to enterocyte damage.[65] In rare cases, patients with SIBO develop D-lactic acidosis, due to proliferation of bacteria producing D-lactic acid. The overgrown bacteria may translocate to the bloodstream and cause bacteraemia.[66] Previous studies showed that weaning off PN is more difficult in children with SIBO.[67,68] The diagnosis of SIBO is often empirically made and improvement in symptoms after treatment is seen as confirmation of the diagnosis. The management of SIBO consists of treating risk factors, correcting nutrient deficiencies and suppressing abnormal colonization with antibiotics or probiotics.[64] Reducing dosages of antisecretory and antimotility drugs should be considered.[41]

Antibiotics

Antibiotics commonly used are metronidazole, ciprofloxacin, rifaximin, amoxicillin/clavulanic acid, doxycycline, neomycin and tetracycline, mostly prescribed for 7-14 days.[41] When chronic prescription is necessary, drug-free intervals may be recommended such as 3 weeks on, 1 week off. Drug rotation may prevent the development of resistant bacterial strains. Antibiotics are preferably given enterally. No RCTs on the safety and efficacy of different antibiotics in SBS have been reported.

Probiotics

Limited evidence from studies using different probiotics suggests that probiotics might increase the rate of height and weight gain and improve the faecal microbiota of children with SBS.[69] However, cases of bacteraemia with the prescribed probiotic bacteria in infants with SBS have also been reported.[70] Since the effect of probiotics in patients with SBS has not yet been adequately assessed, the routine use of probiotics is not recommended.[69]

Growth factors

In the past decade, much attention has been paid to the development and use of intestinal growth factors that could stimulate intestinal adaptation.

Growth hormone and glutamine

Growth hormone (GH) is produced in the anterior pituitary gland, binds to GH receptors present throughout the intestine and stimulates the production of insulin like growth

factor (IGF)-1. In 2003, somatropin, a recombinant form of human GH, was approved for short-term treatment of adults with SBS receiving specialized nutrition support.

Human GH and glutamine, the primary fuel for enterocytes, are believed to act synergistically on intestinal adaptation. Several RCTs on the effect of recombinant human GH alone or combined with glutamine in adults with SBS[71-75] reported improved body weight[72-75], lean body mass[72,73] and increased intestinal absorption at the end of treatment.[72-74] The latter, however, was not found when measured five days after GH discontinuation.[75] In a more recent RCT[71], patients receiving somatropin and glutamine and patients receiving somatropin with glutamine placebo had greater reductions of PN volume than patients receiving glutamine alone. However, three months after completion of the study, body weight of all patients was lower than that at baseline.[71]

The effect of somatropin is mainly related to increased wet weight absorption (fluid retention), while the effect on energy absorption is minor. Furthermore, the effect seems especially present when the colon is in continuity. A Cochrane review from 2010 concluded that there is insufficient evidence for recommending GH because the positive effect was only temporary in most trials.[76] The European Society of Parenteral and Enteral Nutrition (ESPEN) Guideline on Parenteral Nutrition does not recommended routine use of GH.[77] Additionally, there is no conclusive evidence that the addition of glutamine enhances the effect of GH.[76] Moreover, the use of glutamine alone to stimulate adaptation is not supported by sufficient evidence.[78]

In children, the effect of GH remains unknown. In a RCT in 14 children with SBS, GH treatment during 8 months versus 4 months did not improve weaning off PN.[79] A non-randomized trial[80] showed that a 12-week recombinant human GH treatment led to a decrease in PN, but only 2/8 children could be definitively weaned from PN.

Glucagon-like peptide 2

Glucagon-like peptide-2 (GLP-2) is produced by the enteroendocrine L cells, predominantly found in the ileum and colon.[81] GLP-2 leads to villous hyperplasia, stimulation of crypt cell growth, reduced enterocyte apoptosis and increased intestinal absorption.[82] Furthermore, it inhibits gastric acid secretion and gastric emptying, stimulates intestinal blood flow, increases intestinal barrier function, has anti-inflammatory characteristics and may decrease bone resorption.[82]

A proof-of-concept study in adults with an end-jejunostomy showed that GLP-2 improved intestinal energy and wet weight absorption and increased body weight (reviewed in [82]). Since GLP-2 is rapidly inactivated, an alternative was developed, the recombinant human GLP-2 analogue teduglutide. This was approved in 2012 for the treatment of adults with SBS dependent on PN despite optimal medical therapy. The recommended dose

is 0.05 mg/kg administered subcutaneously once daily. Two phase III clinical studies with teduglutide have been performed.[83,84] In one, patients receiving teduglutide at the recommended dose had greater PN volume reductions than patients receiving placebo.[83] Although these patients received less PN, their body weight gain was significantly higher than that of patients receiving placebo.[83] Small bowel biopsies showed that teduglutide increased villous height and crypt depth.[82] In a 28-week open-label extension study[85], a mean PN reduction of 52% from baseline levels was shown. In the other phase III clinical study, a placebo-controlled RCT in 68 adults[84], patients treated with teduglutide for 24 weeks had significantly higher PN reductions, associated with improvements in quality of life.[86] The consecutive open-label study showed that teduglutide also reduced PN volume after 2 years (reviewed in [82]).

In contrast to adults, studies with teduglutide in children are scarce. A study on the pharmacokinetics and safety of a GLP-2 analogue in children with IF was recently published.[87] Seven children received GLP-2 subcutaneously during 6 weeks. GLP-2 was well tolerated, and the pharmacokinetic profile was similar to that of adults.[87] Furthermore, an open-label study was performed in 42 children with SBS, receiving 0.0125, 0.025 or 0.05 mg/kg/day teduglutide or standard of care.[88] At week 12, the mean prescribed PN volume decreased, with the greatest effect of 0.05 mg/kg/day. Four patients achieved intestinal autonomy (3 with 0.05 mg/kg/day). However, two of them resumed PN 4 weeks thereafter.

One study regarding the combination of GLP-2 and GLP-1 showed that this led to additional beneficial effects on intestinal absorption compared to either drug given alone.[89]

Other growth factors

A number of other growth factors have shown effect in animal studies, including insulin[90], endogenous serine protease dipeptidyl peptidase IV[91], epidermal growth factor (EGF)[92], IGF-1[93] and hepatocyte growth factor.[94] Insulin and EGF have also been tested in humans. In an open-label pilot study in children with SBS, oral or enteral insulin increased EN, though not statistically significant.[95] Two of the ten children were weaned off PN. EGF administration in five children with SBS was associated with a significant improvement in carbohydrate absorption and percentage of calories received enterally.[96] Further research should determine the role of these growth factors in patients.

SUMMARY

Intestinal adaptation is the natural compensatory process that occurs after small bowel resection. The aim of this review was to provide an overview about the nutritional strategies and medication that best promote this process.

In terms of promoting intestinal adaptation, human milk or polymeric nutrition (containing whole protein, complex carbohydrates and long chain triglycerides) is recommended, depending on the age of the patient. However, on individual indication such as absence of specific parts of the bowel, the EN composition should be adjusted if necessary. At least a part of EN should be given continuously, while to preserve oral skills small amounts of oral feeds should be given.

Routinely used medications in SBS patients are antisecretory and antidiarrheal medication, prokinetic drugs and antibiotics to treat bacterial overgrowth. There is, however, a great variability in the application of these drugs and the scientific evidence is limited. Regarding growth factors used to promote intestinal adaptation, the GLP-2 analogue teduglutide is suitable for adults with SBS dependent on PN despite optimal medical therapy. Other growth factors, such as growth hormone, are not recommended for routine use.

Further research is necessary to investigate the best EN composition to promote intestinal adaptation. Additional evidence regarding the effectivity and safety of teduglutide in children needs to be provided before it can be used in clinical practice. Trials on the effectiveness of certain nutrition and medication strategies in patients with SBS are complicated by the fact that it is hard to tell whether the effects on intestinal adaptation are actually due to the intervention or the normal clinical course of intestinal adaptation.

PRACTICE POINTS

- Due to heterogeneity in terms of age of the patient, residual bowel anatomy and nutritional requirements, management of patients with SBS is highly complex and individualized.
- To promote intestinal adaptation, human milk or polymeric formula (containing whole protein, complex carbohydrates and long chain triglycerides) is recommended, depending on the age of the patient.
- On individual indication such as the absence of specific parts of the bowel, the EN composition should be adjusted if necessary.
- At least a part of EN should be given continuously, while to preserve oral skills small amounts should be given orally.
- Routinely used medications to reduce factors that complicate the adaptation process are antisecretory and antidiarrheal medication, prokinetic drugs and antibiotics to treat small intestinal bacterial overgrowth.
- The GLP-2 analogue teduglutide is suitable for adults with SBS dependent on PN despite optimal medical therapy. Recombinant human growth hormone is not recommended for routine use.

RESEARCH AGENDA

- Determining the best composition of enteral nutrition.
- Evaluating the effectivity and safety of antibiotics and probiotics used to treat SIBO.
- Further evidence for the effectivity and safety of GLP-2 analogue in children.
- The value of the promising growth factors arising from animal models for the treatment of patients with SBS.

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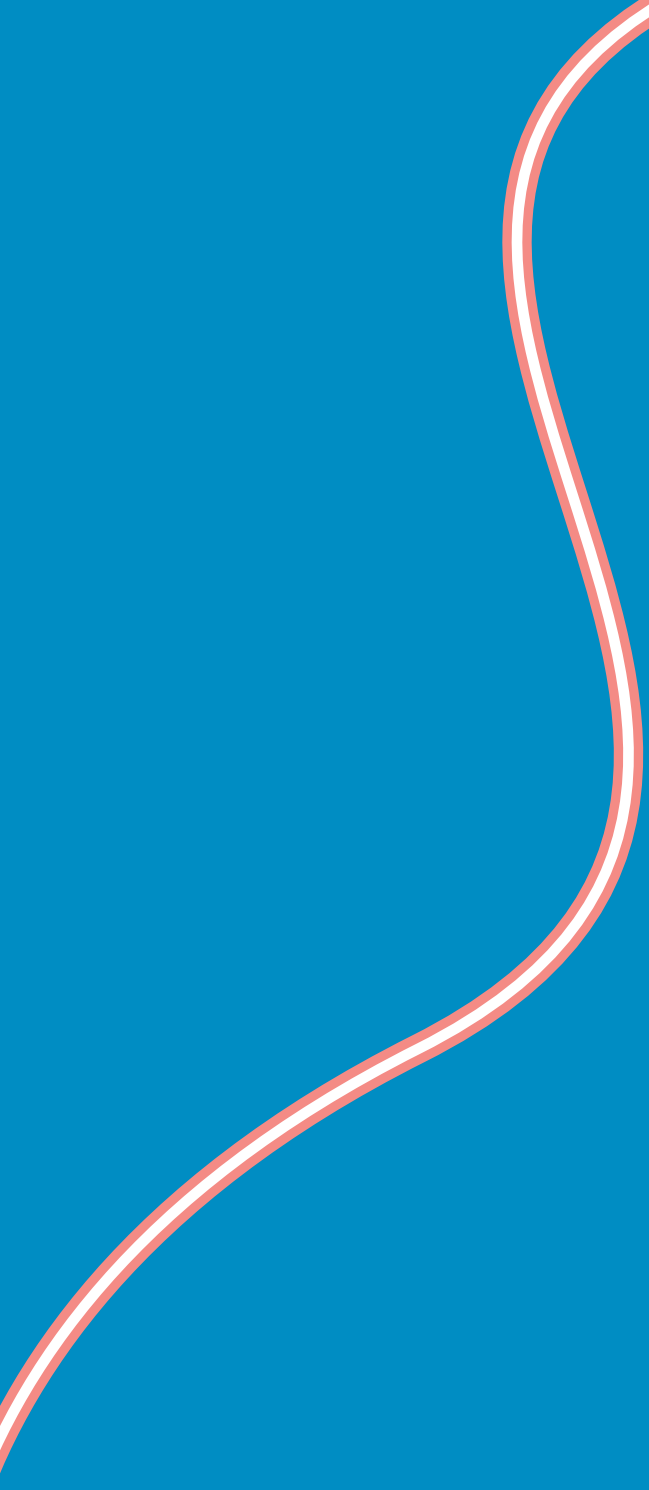

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Growth, body composition, and micronutrient abnormalities during and after weaning off home parenteral nutrition

J Pediatr Gastroenterol Nutr. 2018 Nov;67(5):e95-e100.

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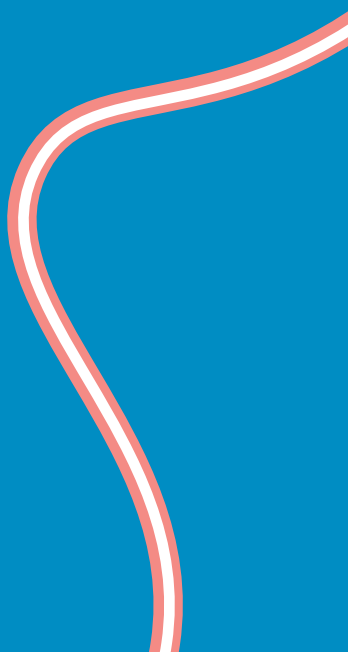


ABSTRACT

Objectives

The aim of this study is to assess growth, body composition, and micronutrient abnormalities in children with intestinal failure (IF) over time, both during and after weaning off parenteral nutrition (PN).

Methods

Retrospective study in children on home PN between 2001 and 2015. Weight-for-age (WFA) and height-for-age (HFA) SD scores (SDS) were calculated, as well as fat mass (FM) and fat free mass (FFM) SDS obtained by dual energy X-ray absorptiometry. The course of growth parameters and body composition was analyzed with linear mixed models. All micronutrient measurements during the study period were obtained.

Results

Fifty-two patients were included with a median follow-up of 3.4 years. Seventy-one percent weaned off after a median PN duration of 0.9 years. One year after the start of PN, 28 patients were still PN-dependent with median WFA-SDS of -0.66 and median HFA-SDS of -0.96, both significantly lower than zero. Catch-up growth was achieved during PN, but HFA-SDS decreased after weaning (p=0.0001). At a median age of 6.2 years, median %FM SDS was 0.30 and FFM SDS was -1.21, the latter significantly lower than zero. Frequent micronutrient abnormalities during PN were vitamin A (90%), zinc (87%), and iron (76%) and after weaning vitamin A (94%), E (61%) and 25-OH vitamin D (59%).

Conclusion

Children with IF demonstrate abnormal growth and body composition and frequent micronutrient abnormalities. Longitudinal evaluation showed that catch-up growth occurs during PN, but height SDS decreases after weaning. This underlines the need for close monitoring, also after reaching enteral autonomy.

INTRODUCTION

Intestinal failure (IF) is defined as a critical reduction of the gut mass or function, below the minimum needed to absorb nutrients and fluids.[1] In order to grow and develop, children with IF are dependent on parenteral nutrition (PN). Despite the treatment with PN, growth failure is an important problem in these children. Previous studies have shown that almost 50% of the children receiving long-term PN have a height below the normal range for age and that they are significantly lighter and shorter than healthy children.[2,3] In current clinical practice, growth monitoring of children with IF is mainly based on the quantity of growth by measuring weight and height, whereas body composition such as the amount of fat mass (FM) and fat-free mass (FFM) is not routinely measured. A previous study showed that children with IF had a significant deficit in limb lean mass, with high FM in children totally PN-dependent.[4] Abnormal body composition can be associated with cardiovascular and metabolic risks[5], but also with muscle weakness and reduced bone accretion.[6]

Next to growth failure, children with IF are at risk of micronutrient abnormalities.[7,8] Factors that may contribute are malabsorption, resection of specific parts of the bowel, and inflammation.[9,10]

Although previous studies focused on growth and body composition in a cross-sectional way, our aims were to assess the course of growth parameters and body composition over time and to quantify the prevalence of micronutrient abnormalities in children with IF, both during and after weaning off PN.

METHODS

Study population

This was a single-center retrospective study evaluating all children receiving home PN (HPN) between January 2001 and January 2015. Patients were divided into functional (enteropathies and motility disorders) and surgical IF. The category surgical IF consisted of children with short bowel syndrome (SBS) and children after small bowel resection with a remaining small bowel length not as short as covered by the SBS definition. SBS was defined according to the Dutch National Working group Pediatric SBS[11] as a resection of ≥70% of the small bowel and/or a remaining small bowel length measured distal to the ligament of Treitz <50 cm, <75 cm and <100 cm in preterm infants, term infants, and children >1 year, respectively.

Approval of the local research ethics committee was obtained (MEC-2014-341). Since the retrospective data were analyzed anonymously, written informed consent was not necessary.

Data collection

We collected data from start of IF until January 2015 by reviewing the hospital records, including patient and bowel characteristics, nutritional data, growth and body composition data. Start of IF was defined as the date of bowel resection for surgical IF and start date of PN for functional IF.

Nutritional data

Children on HPN were frequently seen at our outpatient clinic, but also after weaning off PN they visited the outpatient clinic at least yearly for growth monitoring, evaluation of nutritional intake, and laboratory evaluation of micronutrients. Weaning off PN was started when sufficient amounts of enteral/oral nutrition were tolerated. Patients were considered partially PN-dependent when receiving <80% of their calories via PN, and weaned off PN when they received full enteral/oral nutrition and did not restart PN before the end of the study. Weaning off PN was only performed when growth was acceptable (height within target height range and weight and height between -2 and +2 standard deviation score (SDS)) and SDS of weight and height did not deviate from the individual's previous growth curves while on PN. PN was described according to the ESPGHAN/ESPEN guideline[12] and nutritional intake was adjusted according to growth. For the patients included, the micronutrient supplementation parenterally received was Vitintra Infant®, Soluvit®, Peditrace® (<10 kg) and Addamel® (10-30 kg), customized as needed by the pharmacy. Micronutrients were supplemented either parenterally or enterally/orally according to the ESPGHAN/ESPEN guideline[12] and individually adjusted according to the measured levels, also after weaning.

Growth and body composition

Weight and height were measured using standard equipment. Sex- and age-adjusted SDS were calculated for weight (weight-for-age (WFA)/weight-for-height (WFH)) and height (height-for-age (HFA)) by using the up to date Dutch national reference standards[13] using the Growth Analyzer Research Calculation Tool.[14] The Fenton preterm growth charts were used until the gestational age of 40 weeks.[15] Afterwards, a corrected age was used until 2 years of age. Height and weight data were collected at 3, 6, 9, 12, 18 and 24 months after start of PN and afterwards on annual basis. When measurements were not available on the assigned day, the measurement closest to that day was chosen or noted as a missing value when there was no measurement available within 1 month. Additional measurements were collected if no measurements were available at the designed time points for the linear mixed model analysis (see statistical analysis). Target height (TH), TH SDS and 95% TH range (± 1.6 SD range) were calculated with use of parental heights.[16]

Body composition data were obtained via dual energy X-ray absorptiometry (DEXA) scans, performed as routine care starting from around age 5, in order to monitor bone health. SDS for percentage fat (%FM) and absolute FFM were calculated using Dutch reference data, available for children ≥4 years of age.[17] Growth and body composition SDS <-2 were defined as abnormal.

Micronutrients

The micronutrients examined were: vitamin A, B1, B6, total vitamin B12, 25-OH vitamin D, vitamin E, aluminium, chromium, copper, selenium, zinc, iron, and ferritin. All measurements during the study period were collected and interpreted as normal or abnormal. If during the study period >1 micronutrient level was obtained in 1 patient, the most abnormal level (high or low depending on the micronutrient) on PN and the most abnormal level weaned off was identified as indicative of abnormality status. Children were clinically stable during micronutrient assessment, without signs of line sepsis or increased C-reactive protein.

Statistical analysis

Statistical analyses were performed using SPSS Version 21.0 (Armon, NY: IBM Corp). Categorical data are summarized as frequencies and percentages and continuous data as median and interquartile range (IQR) or range. Differences in anthropometrics between patients on PN and patients weaned off were assessed using the Mann-Whitney *U* test and Fisher's exact test. To determine whether growth and body composition SDS differed significantly from healthy children, the Wilcoxon one-sample test was used. Spearman's correlation analysis was used to examine relationships between growth and body composition. The Fisher's exact test was used to compare the prevalence of micronutrient

abnormalities between children totally versus partially PN-dependent as well as functional versus surgical IF.

To evaluate the course of growth and body composition during and after weaning off PN we used linear mixed effect models. Mixed models appropriately account for the correlations in the repeated measurements of each subject. In addition, the provide valid inferences under the missing at random missing data mechanism. Moreover, they allow for measurements to be taken at different time points per patient, and appropriately model the longitudinal evolutions of each outcome. A linear mixed effects model was built for each of the 3 growth parameters, only including the patients that were able to wean. In the specification of these models we allowed the longitudinal evolutions to change after PN was stopped for each child. Moreover, we also allowed for potential nonlinear evolutions per parameter. To accommodate these features we used natural cubic splines of time, which explicitly allowed for a change in the evolutions after PN stopped. These terms were included both in the fixed and random-effects part of the models. To select the optimal random-effects structure and test whether the longitudinal evolutions were nonlinear we used likelihood ratio tests. To test whether there was a change in the longitudinal evolutions after PN we used an F-test. In addition, residuals analysis was performed to evaluate the models' assumptions. In the 12 patients with various subsequent HPN periods, a stop period of ≥6 months was seen as a definite stop for this analysis. The weight and height measurements of patients with a stop period <6 months were included in the analysis of growth on PN. For body composition, the fixed-effects part included the covariates duration of PN, time intervals between start of PN and the measurements, and WFH-SDS. For the random-effects part random intercepts were included. The optimal random-effects structure was chosen using the Akaike information criterion, while for the fixed-effects p-values were based on t- and F-tests.

Statistical significance was set at p-value of 0.05. In case of multiple comparisons, an adjusted significance level was used according to the Bonferroni correction (significance level =0.05/number of comparisons).

RESULTS

Patient characteristics

Between 2000 and 2015, 62 children received HPN. Three patients deceased and 7 had their follow-up at another hospital, leading to 52 included patients with available follow-up data. Patient characteristics are shown in **Table 1**. Twenty patients (38%) had SBS. Thirty-seven patients (71%) weaned off PN after a median PN duration of 0.92 years. The median follow-up duration until January 1, 2015 was 3.35 years (IQR 1.53 – 6.61).

Table 1. Patient characteristics of children with intestinal failure receiving home parenteral nutrition

	n = 52 n (%) or median (IQR)	**Able to wean off PN n = 37**	**Not able to wean off PN n = 15**	**p-value**
Sex: female	29 (56)	22 (60)	7 (47)	NS
Prematurity (gestational age < 37 weeks) – n (%)	32 (62)	23 (62)	9 (60)	NS
Age at start of IF (days) – median (IQR)	6 (0 – 42 days, range 0 – 16 years)	3 (0-31)	18 (3-47)	NS
Category of IF – n (%)				NS
Surgical	41 (79)	32 (87)	9 (60)	
SBS, remaining small bowel length – median cm (IQR)	20 (49), 40 (22 – 49)	14 (38), 60 (45-80)	6 (40), 28 (16-70)	
Functional	11 (21)	5 (14)	6 (40)	
Enteropathy	8 (72)	4 (80)	4 (67)	
Motility disorder	3 (27)	1 (20)	2 (33)	
Underlying diseases – n (%)		NA	NA	NA
Intestinal atresia	11 (21)			
Necrotizing enterocolitis	10 (19)			
Volvulus	5 (10)			
Gastroschisis	5 (10)			
Gastroschisis with atresia	2 (4)			
Ileus	4 (8)			
Intestinal lymphangiectasia	2 (4)			
Other	13 (29)			
Ileocecal valve in situ – n (%)	34 (65)	25 (68)	9 (60)	NS
Colon in situ – n (%)	43 (83)	30 (81)	13 (87)	NS
PN duration until weaning off PN or until end of study if not able to wean, years – median (IQR)		0.92 (0.52 – 1.87)	2.36 (0.78 – 5.09)	NA
Age at weaning or end of study if not able to wean, years – median (IQR)		1.41 (0.61 – 2.81)	2.74 (1.23 – 7.96)	NA

Abbreviations: IF, intestinal failure; NA, not applicable; NS, not significant; PN, parenteral nutrition; SBS, short bowel syndrome.

Growth

In total, 597 weight (median per patient 8) and 504 height measurements (median per patient 8) were obtained. For the cross-sectional analysis at one year after start of PN (with a range of 1 month before and after) growth data were available for 41 patients (**Supplemental Figure 1**). Twenty-eight patients (68%) were still dependent on PN and had a median WFA-SDS of -0.66, median HFA-SDS of -0.96, and median WFH-SDS 0.06 (**Table 2**); both WFA-SDS and HFA-SDS were significantly lower than zero. For children weaned off PN, WFA-SDS was significantly lower than zero. There were no significant differences between growth parameters of children on PN and children weaned off PN at 1 year after start of PN. In addition, no significant differences between children with surgical IF and functional IF were found.

Table 2. Growth outcomes according to Dutch reference standards at 1 year after start of parenteral nutrition

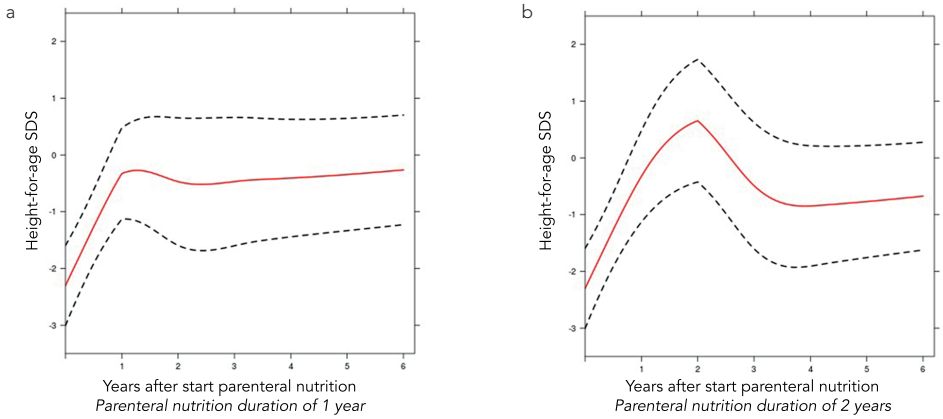
	Children on PN (n = 28)		Children weaned off PN (n = 13)	
	n		n	
WFA-SDS	28		13	
median (IQR)		-0.66 (-1.07 to -0.07)*		-0.89 (-1.76 to 0.21)*
< -2 (n (%))		4 (14)		2 (15)
HFA-SDS	27		13	
median (IQR)		-0.96 (-1.68 to -0.07)*		-0.33 (-1.56 to 0.25)
< -2 (n (%))		6 (21)		1 (8)
WFH-SDS	27		13	
median (IQR)		0.06 (-0.79 to 0.88)		-0.37 (-1.29 to 0.37)
< -2 (n (%))		2 (7)		0 (0)
> +2 (n (%))		1 (4)		0 (0)

Legend: * significantly lower than zero.
Abbreviations: HFA, height-for-age; PN, parenteral nutrition; WFA, weight-for-age; WFH, weight-for-height.

Differences between actual height and TH could be calculated in 23 of 52 patients, at a median age of 2.1 years, 2 years after start of PN. Missing values were due to absence of the child's height or height of one of the parents. Median distance between actual HFA-SDS and TH SDS was -0.26 (IQR -0.87 to 0.85), whereas 2/23 patients were growing below their TH range.

Linear-mixed models showed that the course of HFA-SDS was significantly different during and after weaning off PN (p=0.0001). **Figure 1** illustrates the course of HFA-SDS during and after weaning off PN according to the model, with different PN durations of 1 and 2 years. Visual inspection of this graph shows that median HFA-SDS was low at start of IF, but that catch-up growth occurred during PN, with a decrease in HFA after weaning off PN. For WFA-SDS (**Supplemental Figure 2**) and WFH-SDS the course of growth was not different during and after weaning off PN, with catch-up growth during PN, but stable values after weaning (data not shown).

Figure 1. Course of HFA-SDS during and after weaning off PN



Legend: Figure 1a illustrates the linear mixed effect model of the course of HFA-SDS in children with IF during and after weaning off PN with a PN duration of 1 year. Figure 1b illustrates the linear mixed effect model of the course of HFA-SDS during and after weaning off PN with a PN duration of 2 years. Red line represents median, dotted lines represent 95% confidence interval.
Abbreviations: HFA, height-for-age; IF, intestinal failure; PN, parenteral nutrition.

Body composition

Nineteen children (37%) underwent a DEXA scan as standard follow-up to monitor bone health (52% of the children were too young i.e. <4 years of age). For children with multiple DEXA scans, the results of the first DEXA scan were analyzed. The first DEXA scan was made at a median age of 6.2 years (IQR 5.4 – 9.3). At that time 13 patients (68%) were already weaned off PN, whereas 6 were still partially dependent on PN. Median HFA-SDS was -0.66, WFA-SDS -0.74 and WFH-SDS -0.68 (**Supplemental Figure 3**). Median FFM SDS was -1.21 (IQR -1.93 to -0.87), which was significantly lower than zero (p<0.001). Median %FM SDS was 0.30 (IQR -0.26 to 1.26), which was not significantly different from zero (p=0.08). FFM SDS was significantly positively associated to WFA-SDS (Spearman's rho 0.613, p=0.009) and HFA-SDS (0.744, p<0.001). For %FM SDS, only WFH-SDS was significantly correlated (0.515, p=0.034).

Nine patients had multiple DEXA scans with a maximum of 8 scans. Using linear mixed models, course of WFH-SDS was positively associated with the course of %FM SDS over time with an increase of 0.7 SD in %FM for each 1 SD increase of WFH (p<0.001). For FFM SDS, no significant associations were found.

Micronutrient deficiencies

Table 3 shows the frequency of micronutrient monitoring during and after weaning off PN and the prevalence of abnormalities. There were no differences in the prevalence of abnormalities between children totally versus partially PN-dependentor surgical versus functional IF.

Table 3. Micronutrient monitoring and prevalence of micronutrient abnormalities during and after weaning off PN

Micronutrient (reference range)	Patients assessed during PN	Deficiency during PN	Patients assessed after weaning	Deficiency after weaning
	n	n (%) Median level of patients with deficiency (range, IQR)	n	n (%) Median level of patients with deficiency (range, IQR)
25-OH vitamin D (50 - 120 nmol/L)	24	10 (42) 40.5 (20.0 – 48.0, IQR 34.5 - 44.3)	18	10 (56) 30.5 (5.0 – 46.0, IQR 13.3 - 42.8)
Total vitamin B12 (145 - 637 pmol/L)	29	2 (7) 71 (22 - 120, IQR NA)	18	4 (22) 87 (42 - 127, IQR 52 - 119)
Vitamin B1 (70 - 140 nmol/)	22	0 (0)	15	1 (7) 61 (range and IQR NA)
Vitamin B6 (35 - 100 nmol/L)	20	0 (0)	15	0 (0)
Vitamin A (1.25 - 3.00 µmol/L)	31	28 (90) 0.67 (0.22 - 1.16, IQR 0.47 - 0.89)	18	17 (94) 0.83 (0.33 - 1.21, IQR 0.62 - 0.97)
Vitamin E (16.5 - 41.6 µmol/L)	31	12 (39) 11.4 (5.4 - 15.4, IQR 7.4 - 13.4)	19	12 (63) 10.5 (5.1 - 13.8, IQR 9.2 - 12.6)
Aluminum (< 0.36 µmol/L or < 21 µg/L)	18	0 (0)	6	0 (0)
Chromium (< 40.4 nmol/L)	12	0 (0)	3	0 (0)
Copper (9.6 - 20.1 µmol/L)	23	2 (9) 8.3 (8.0 - 8.6, IQR NA)	13	0 (0)
Selenium (63 - 142 µg/L)	19	3 (16) 45 (30 - 48, IQR NA)	13	3 (23) 44 (25 - 58, IQR NA)
Zinc (64.3 - 124 µmol/L)	23	20 (87) 13.9 (6.0 - 56.0, IQR 11.0 - 37.4)	16	11 (69) 13.0 (6.0 - 56.0, IQR 7.0 - 49.5)
Iron (5 - 3 µmol/L, < 1 year; (10 - 30 µmol/L, > 1 year)	45	34 (76) 4.1 (1.5 - 14.3, IQR 3.2 - 4.6)	20	13 (65) 4.4 (2.0 - 8.3, IQR 3.2 - 7.2)
Ferritin (30 - 240 µg/L)	48	22 (46) 8.5 (4.0 - 24.0, IQR 5.8 - 15.0)	21	6 (29) 7.5 (4.0 - 26.0, IQR 4.8 - 16.3)

Legend: Total patients in follow-up: 52 during PN, 37 after weaning of PN.
Abbreviations: IQR, interquartile range; NA, not applicable; PN, parenteral nutrition.

DISCUSSION

This study aimed at evaluating the course of growth parameters and body composition and the prevalence of micronutrient abnormalities, during and after weaning off PN. Our study shows that 1 year after the start of PN, children with IF had a significantly lower weight than healthy children. When still on PN, children were also significantly shorter. In addition, children had lower FFM than healthy controls at their first DEXA. Moreover, this study is the first to evaluate the longitudinal course of growth during and after weaning off PN using linear-mixed models, showing catch-up growth during PN, but a significant decrease of HFA-SDS after weaning.

We found that children with IF were significantly shorter and lighter 1 year after the start of PN, and still lighter after weaning off PN compared to the healthy Dutch growth reference population. Our results are comparable with a previous study by Raphael et al.[18] Another study[19], however, reported normal growth measurements in weaned children, which may be explained by their small sample size and the fact that weaning took place for >2 years at time of assessment.

Of the growth parameters measured, height was impaired the most. This has been reported previously.[2-4] Seventeen percent of the children had a height below the normal range for age 1 year after the start of PN. This is lower than the 50% reported by Pichler et al.[2], which may be explained by the fact that in that study almost all children were still (partially) dependent on PN (median time of 5 years) implying more severe IF, whereas in our study already one third was weaned off PN within 1 year. Our children were, however, not growing as expected based on their TH SDS, shown as negative median distance between actual HFA-SDS and TH SDS. Longitudinal evaluation showed catch-up growth during PN for all growth parameters, but a significant decrease of HFA-SDS after weaning, especially after a PN duration of 2 years. The fact that the course of WFA and WFH was not significantly altered after weaning suggests that patients weaned off PN receive enough oral/enteral nutrition to maintain their weight, but may suffer from persistent chronic malabsorption, and should maybe receive more nutrition (enteral or even parenteral) in order to maintain their linear growth course. Most important, this emphasizes the need for continuing follow-up after achieving enteral autonomy including a possible individualized nutritional intervention at a later stage after weaning especially in times of increased growth velocity such as puberty.

When monitoring growth, it is also important to evaluate body composition. As a result of the low HFA in children with IF, WFH was not significantly different from healthy children. This could imply a good body composition, but when looking at the actual body composition results, patients had significant lower FFM, even when most of the children were already weaned off PN at the first measurement. This is in agreement

with the previous study covering this topic.[4] Possibly due to the small sample size, FM was not significantly higher than in healthy references. Monitoring body composition is valuable since abnormal body composition is associated with several determinants of cardiovascular disease, type 2 diabetes mellitus and metabolic syndrome.[5,20,21] In addition, FFM is one of the strongest predictors of bone mass.[6,22,23] Studies assessing body composition from diagnosis onwards are therefore necessary to determine what optimal growth in children with IF is.

Micronutrient abnormalities were commonly present during treatment with PN, but also after weaning. Reasons for these abnormalities will vary depending on the level of PN dependency and the existing degree of malabsorption of EN and enteral micronutrient supplements after weaning of PN. Especially fat-soluble vitamins were frequently deficient, which might be caused by fat malabsorption due to ileal resection, cholestasis or the use of cholestyramine. Our results are generally in agreement with previous studies, although we found higher prevalence of abnormalities of most micronutrients.[7,8,24-27] In general, it is assumed that the micronutrient preparations in PN meet the nutritional requirements for totally PN-dependent children. As abnormalities were also found in children totally PN-dependent, we suggest reevaluation of micronutrient content in PN, especially for use in children on long-term PN.

Strikingly, not all micronutrients were monitored regularly, as no strict protocol was followed during the study period. It is therefore possible that monitoring was mainly performed in selected patients considered at high risk of abnormalities. Guidelines on micronutrient monitoring in children with IF vary widely and are not specific for weaned patients[12], but usually regular monitoring is recommended since most patients will not have clinical symptoms. In a recent paper, it is suggested that copper, selenium, zinc, vitamin A, E, D, B12, methylmalonic acid, prothrombin time, iron, total iron-binding capacity, red blood cell count, folate, and carnitine (the latter if <1 year) should be monitored every 6 months in children on HPN.[28]

Overall it is remarkable that despite frequent involvement of a multidisciplinary team caring for children with IF both during PN and after weaning, abnormalities in growth and micronutrients were found. This may partly be explained by underlying diseases or comorbidity rather than nutritional intake alone. Strict monitoring will, however, ensure timely diagnosis and adequate treatment, including micronutrient supplementation, or (re)start of enteral/PN if necessary.

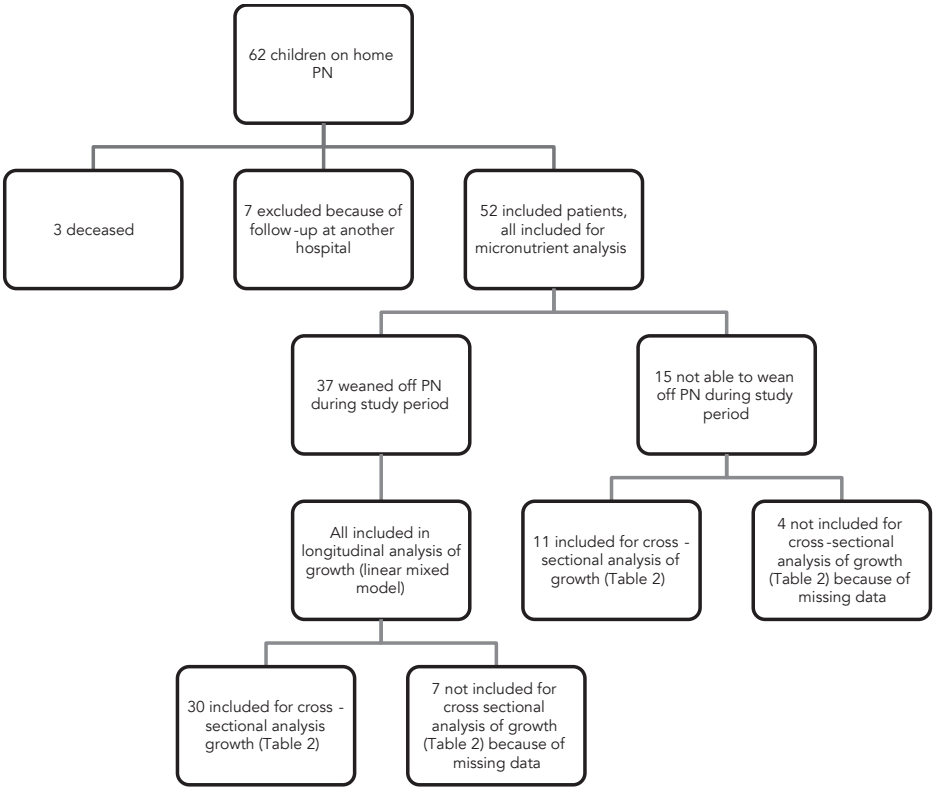
The strengths of our study were the longitudinal design and the high number of growth measurements obtained which allowed for the linear mixed modeling analyses that give insight into the evaluation of growth over time during PN and after weaning. The main limitation of this study is its retrospective design. Detailed information on important

factors that may influence growth, body composition and micronutrient levels, such as quality of PN and enteral/oral micronutrient supplementation could not be systematically collected and therefore not be taken into account. The fact that we did not find any differences in growth or micronutrient abnormalities between children totally and partially PN-dependent or with a different type of IF could also be due to the relative small sample size. Large prospective studies according to a strict protocol are necessary to give more insight into these problems, in order to be able to relate growth, as well as bone age, body composition and micronutrient abnormalities.

In conclusion, this retrospective study showed that despite frequent monitoring, abnormalities in growth, body composition and micronutrients were common both during PN and after weaning. This may have large health implications later in life. With continuing improvement of prognosis, maintaining normal growth and body composition and adequate micronutrient levels become increasingly important in these children and necessitate monitoring by health care professionals, also after weaning. Future prospective studies should focus on what growth target is should be aimed for in relation to achieving an optimal body composition and optimal development.

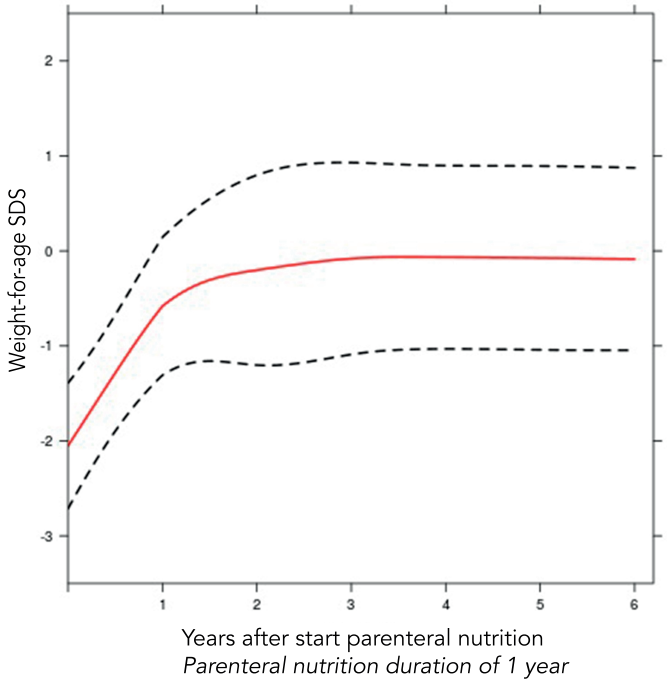
SUPPLEMENTARY MATERIAL

Supplemental Figure 1. Flow chart of patient inclusion



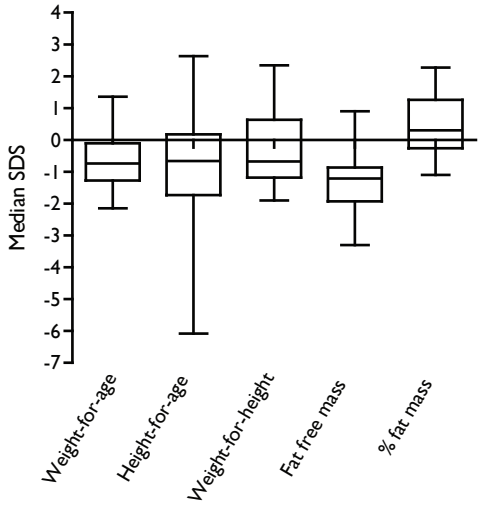
Abbreviation: PN, parenteral nutrition.

Supplemental Figure 2. Course of WFA SDS during and after weaning off PN



Legend: Figure 2 illustrates the linear mixed effect model of the course of WFA SDS in children with IF during and after weaning off PN with a PN duration of 1 year. Red line represents median, dotted lines represent 95% confidence interval.
Abbreviations: PN, parenteral nutrition; WFA, weight-for-age.

Figure 3. Growth and body composition SDS at first DEXA measurement



Abbreviations: DEXA, dual energy X-ray absorptiometry; SDS, standard deviation scores.

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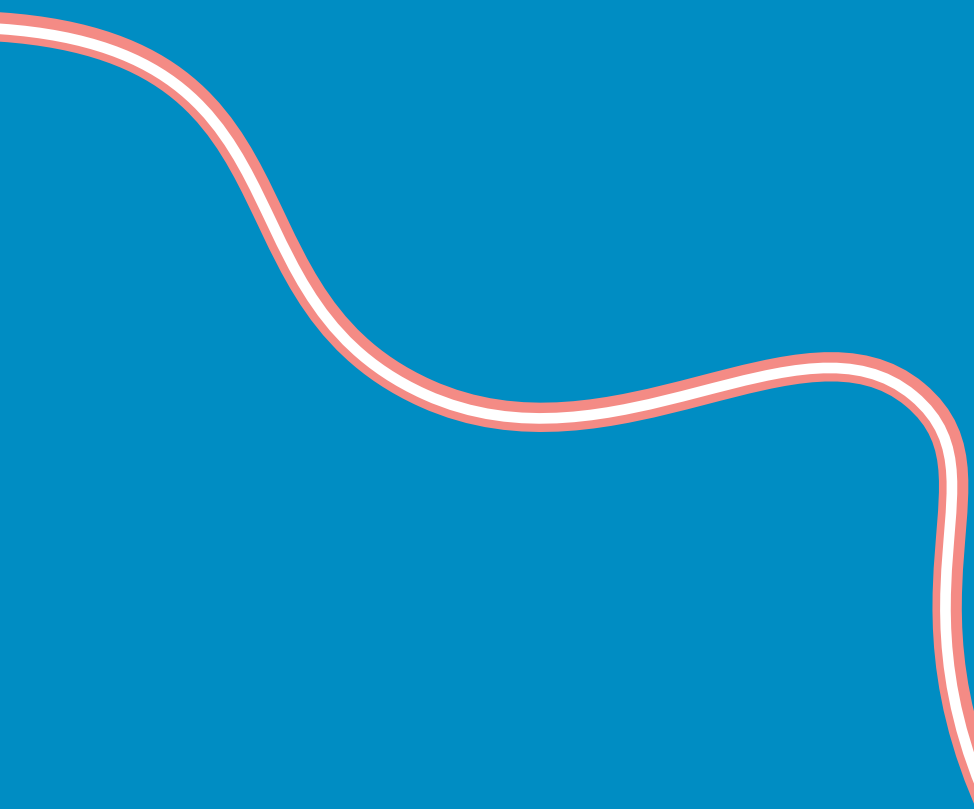

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Body composition using air displacement plethysmography in children with intestinal failure receiving long-term home parenteral nutrition

JPEN J Parenter Enteral Nutr. 2019 Mar 22. doi: 10.1002/jpen.1527.

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ABSTRACT

Background

Children with intestinal failure (IF) are at risk of growth failure, but little information about body composition is available. Our aim was to assess body composition using air displacement plethysmography (ADP) and to relate it to clinical and growth parameters.

Methods

In this prospective descriptive observational 2-center cohort study, children aged 2-18 years receiving home parenteral nutrition (PN) for ≥6 months underwent ADP measurement. Fat mass index (FMI) and fat-free mass index (FFMI) standard deviation scores (SDSs) were calculated to normalize for small body size.

Results

Twenty-one out of 22 children, median age 7.4 years, underwent successful ADP measurement after a median PN duration of 5.5 years. They were significantly lighter (median weight for age SDS -0.71, $p=0.004$) and shorter (median height for age SDS -1.55, $p<0.001$) than the normal population mean; 52% were growing below target height range. They had low FFMI (median SDS -1.53, $p<0.001$) and high FMI (median SDS 0.80, $p=0.002$). Weight for height and body mass index (BMI) were significantly associated with FFMI and BMI with FMI, but children with the same weight and height showed different body composition. In 13 patients with 1-year follow-up, growth and body composition did not change significantly.

Conclusion

Children with IF receiving long-term PN show lower FFM and higher FM than healthy children. Additionally, children with similar routine growth parameters showed different body composition. Further studies should evaluate the effect of a patient-tailored approach including physical activity and nutrition advice based on body composition.

INTRODUCTION

In patients with intestinal failure (IF), the small bowel is too short or dysfunctional and therefore not able to absorb enough nutrients.[1] Consequently, children with IF depend on parenteral nutrition (PN) to maintain growth and development. Current growth monitoring is mainly based on measurements of weight and height and their course over time, and nutrition intake is adjusted accordingly. However, these measurements do not provide information about the quality of growth, i.e. body composition, divided into fat mass (FM) and fat-free mass (FFM). In clinical practice, it is often necessary to increase the amount of PN to improve or maintain linear growth. However, this may result in excessive weight gain rather than improved height, suggesting that FM may be increased rather than FFM.

Previous studies reported that children with IF are significantly lighter and shorter than healthy chidren.[2-5] One study assessing body composition showed that they have a lower FFM.[3] In addition fully PN-dependent patients had increased FM.[3] The assessment of body composition is important because abnormal body composition can be associated with several determinants of cardiovascular disease, type 2 diabetes mellitus, and metabolic syndrome.[6-8] In addition, FFM is one of the strongest predictors of bone mass, which is important because these children are already at risk of poor bone health.[9-13]

Most of the methods available to measure body composition have a number of methodological and practical limitations such as a lack of reference values for young children. Nowadays, body composition can be assessed by air displacement plethysmography (ADP), which is well tolerated by children and does not involve radiation.[14] Our aims were to assess body composition in children with IF receiving long-term PN using ADP and to evaluate the relationship between growth measurements and body composition. Our hypothesis was that children with IF have abnormal body composition, which cannot be detected by standard measurements – i.e., weight and height.

METHODS

Study population

All children on home PN attending the IF teams of the Erasmus Medical Center – Sophia Children's Hospital (Rotterdam, the Netherlands) and the Amsterdam UMC, Emma Children's Hospital, location AMC (Amsterdam, the Netherlands) were asked to participate in a descriptive prospective observational study from March 2015 onwards, which included the measurement of body composition. The minimum PN duration was 6 months, and the minimum age of the patients was 2 years. We included patients who underwent a body composition measurement before May 2018. The study was approved by the local research ethical committees (MEC 2015-002, Dutch Trial Register NTR6080), and informed consent was obtained.

Data collection

Demographic and clinical data obtained from the medical records were age, gender, and underlying disease. Patients were divided into surgical IF and functional IF (including both motility disorders and enteropathies). PN and enteral nutrition were prescribed according to the European Society of Paediatric Gastroenterology, Hepatology and Nutrition and European Society for Clinical Nutrition and Metabolism guideline.[15] Total energy needs were based on calculated total energy expenditure and adjusted over time based on age and routine growth parameters by the IF team dietitians. The dietitians were not aware of the body composition results. The type of parental lipid used was mostly a mixed soybean/medium-chain triglycerides/olive/fish oil lipid emulsion or a mix of olive and soybean oil in case of all-in-one formulations for older children. PN characteristics collected included duration, calories per kg/day, and grams of carbohydrates, lipids, and amino acid infusion per kg/day. In addition, the parenteral glucose infusion rate (milligram glucose/kilogram/minute) and parenteral non-protein energy:nitrogen ratio (nonprotein calories divided by grams of nitrogen) were calculated. Total (parenteral, oral and enteral) energy was also expressed as total calories divided by resting energy expenditure as calculated by the Schofield formula.[16] Percentage PN was used as a measure of PN dependency and was defined as *% of energy provided by PN = (daily energy in kcal provided by PN / total daily energy intake in kcal) * 100*. Full PN dependency was defined as more than 80% of the intake provided by PN, and partial PN dependency was defined as 1-80% of intake provided by PN.[3]

Anthropometrics

Weight and height were routinely measured using standard equipment including a clinical calibrated electronic scale and a stadiometer. Mid-upper arm circumference (MUAC) was measured with a measuring tape at the mid-point between the olecranon and the

acromion of the nondominant arm or of the left arm if the nondominant was not known. Sex-specific standard deviation scores (SDSs) were calculated for weight for age (WFA), height for age (HFA), weight for height (WFH), body mass index (BMI), and MUAC using the latest available Dutch national reference standards (TNO 2010 growth references, for MUAC TNO 2001) and the Growth Analyser Research Calculation Tool, which is a statistical and data analysis software program.[17,18] Target height (TH) in centimeters was calculated as follows for boys: 44.5+0.376×height of the father (cm)+ 0.411×height of the mother (cm). TH was calculated as follows for girls: 47.1+0.334×height of the father (cm)+ 0.364×height of the mother (cm). In addition, TH SDS and 95% TH range (±1.6 SDS) were calculated as described previously.[19,20] HFA/TH SDS, representing a parameter of current height compared with expected height based on parental heights, was calculated by subtracting TH SDS from HFA SDS.[21]

Body composition

Whole-body composition was assessed by ADP based on whole-body densitometry using the BOD POD (BOD POD body composition system including the pediatric option suitable for children above 2 years of age and at least 12 kg, COSMED, Ltd, Concord, CA, USA, **Figure 1**). This method is based on the assumption that the body can be separated into 2 compartments: FM and FFM, the latter including muscle, water, bone, and internal organs. Several studies have shown that ADP is comparable to multicompartment models[14,22-24] and the BOD POD has been validated for the measurement of body composition in children.[22,24,25]

Body composition was measured as soon as possible after obtaining informed consent and 1 year thereafter. All measurements were performed by experienced personnel using a standardized protocol. A detailed description of the BOD POD measurement is provided elsewhere.[22] Patients were assessed wearing tight swimwear, with their hair covered with a bathing cap. Body mass was measured on the integrated electronic scale, and body volume was assessed in the test chamber by applying gas laws that relate pressure changes to volumes of air in the enclosed chamber. The body volume measurement required 2 or 3 tests that lasted 50 seconds each. The 2 body volume measurements that were closest in agreement were used by the system software to calculate the average body volume. Body density was then computed from body mass and body volume and converted to percentage and absolute FM and FFM using sex-specific equations by Fomon and Lohman et al.[26,27] If applicable, the central venous catheter, feeding tube, enterostomy bag, or other additional devices were calibrated in the BOD POD before the measurement. For children up to 6 years of age, a customized seat with adjustable seat tray was used according to protocol.

Figure 1. BOD POD device with customized seat for young children (with permission of COSMED)

As suggested by previous studies[28,29] for accurate assessment of body composition in populations with small body size such as the included group, FM index (FMI) and FFM index (FFMI) were calculated by dividing the FM and FFM in kg by linear height^2 to normalize the body composition variables for body size. The BOD POD itself does not provide SDS, so we calculated age and sex-specific SDS using UK reference values for FFMI and FMI SDS,[30] which were created *de novo* for this study using the lambda-mu-sigma method,[31] which generates centiles by age for outputs taking into account any skew in the data, so that individual SDS can be assigned. We utilized the raw body-density data that were from 533 healthy individuals and used previously to calculate FFM and FM by the 4-component model,[30] along with matching published data on the density of fat-free tissue.[32] These reference data match very closely with our FFMI and FMI reference data published previously, which were calculated using the criterion 4-component model.[30] For children <4 years of age (4 patients at the first BOD POD measurement, none at the second measurement), for whom BOD POD reference data were not available, reference values were obtained from equivalent body composition reference data obtained from deuterium dilution (Wells, Fewtrell, and Cole, unpublished data).

Statistical analysis

Statistical analyses were performed using SPSS Version 21.0 (IBM, Armonk, NY, US). Categorical data are summarized as frequency counts and percentages. Continuous data are

shown as median and interquartile range (IQR) or range. To determine whether growth and body composition differed significantly from that in the reference population, the Wilcoxon 1-sample test (compared with zero) was used. Growth and body composition of children receiving full PN vs partial PN, those with functional vs surgical IF, and boys vs girls were compared with Fisher's exact test and Mann Whitney-U test. The Wilcoxon signed rank test was used to compare growth and body composition at baseline and at 1-year follow-up. Spearman's correlation coefficient was used to correlate growth SDS (WFA, HFA, WFH, BMI and MUAC) with body composition SDS (FMI and FFMI) and PN (duration and macronutrient intake) with growth and body composition SDS. A p-value <0.05 was considered significant.

RESULTS

Patient characteristics

Of 34 children included in the prospective observational study, 22 underwent body composition measurement. Three patients could not be measured because of a body weight <12 kg. In 3 patients, the parents did not agree to the body composition measurement because of general anxiety; in 3 other cases parents did not agree to the measurement because the BOD POD was situated in another hospital (in case of patients treated in Amsterdam). In 3 patients, the body composition measurement was not performed for logistic reasons or because of loss to follow-up. Of these patients, 1 measurement was stopped because the child was distressed. The remaining 21 measurements were considered to be reliable by subjective assessment and were included in the analysis.

Patient characteristics are presented in **Table 1.** The median age at the first body composition measurement was 7.4 years (3.7-17.3). More than half of the patients had functional IF (57%). Chronic intestinal pseudo-obstruction syndrome was the most common underlying disorder (n=6, 29%). At the time of the first body composition measurement, 9/21 patients (43%) were fully PN-dependent. All but 1 of the fully PN-dependent patients had functional IF. The median PN duration at the first BOD POD measurement was 5.5 years. Eighty-six percent of patients received PN every day. Two patients received PN for 6 days a week and 1 patient received PN for 5 days a week.

Anthropometry

Patients with IF were significantly lighter and shorter compared with reference values, with a median WFA SDS of -0.71 (p=0.004) and median HFA SDS of -1.55 (p<0.001) (**Table 2, Figure 2).** One patient had a WFA <-2 (5%), 4 patients had a MUAC SDS <-2 (19%), and 7 patients had a HFA SDS <-2 (33%), indicating chronic malnutrition. None of the patients had WFH <-2 SDS. Eleven patients (52%) were growing below their TH range. Median distance between actual HFA SDS and TH SDS was -1.60 (IQR -2.36 to -0.26). Children with surgical IF had a significantly higher WFH SDS (p=0.049) and BMI SDS (p=0.041). No significant differences in growth characteristics were found between boys and girls or those receiving full vs partial PN. One patient was in puberty, and 1 post pubertal; the remaining patients were prepuberty at time of the body composition measurements.

Body composition

Median FMI SDS was 0.80, and median FFMI SDS was -1.53 (Table 2). FMI SDS was significantly higher than the reference population (p=0.002) whereas FFMI SDS was significantly lower (p <0.001). Thirty-three percent of the patients had a FFMI SDS <-2.

Table 1. Patient and PN characteristics

Characteristic	**n = 21** **n (%)**
Gender: male/female	11/10 (52/48)
Age at start of PN, months – median (range)	1.5 (0 months - 9 years)
Age at first BC measurement, years – median (range)	7.4 (3.7 - 17.3)
Prematurity	8 (38)
Duration of PN at first BC measurement, years – median (IQR)	5.5 years (1.1 - 9.4)
Type of IF	
Surgical IF	9 (43)
Functional IF	12 (57)
Motility disorder	8 (38)
Enteropathy	4 (19)
PN dependency at first BC measurement	
Full PN	9 (43)
Partial PN	12 (57)
% PN – median (IQR)	80 (56 - 100)
PN characteristics at first BC measurement – median (IQR)	
Energy (kcal/kg/day)	53.5 (37.3 - 69.8)
Energy/resting energy expenditure (%)	116 (103 - 158)
Carbohydrate (g/kg/day)	8.4 (4.9 - 11.7)
Glucose infusion rate (mg/kg/min)	5.8 (3.4 - 8.1)
Lipid (g/kg/day)	1.1 (0.8 - 1.6)
Amino acids (g/kg/day)	2.0 (0.8 - 1.6)
Nonprotein calories/nitrogen ratio	129:1 (103:1 - 150:1)
Total calories/resting energy expenditure (%)	167 (145 - 187)

Legend: Full PN dependency was defined as > 80% of the intake provided by PN, and partial PN dependency as 1-80% of intake provided by PN.[3]
Abbreviations: BC, body composition; IF, intestinal failure; IQR, interquartile range; PN, parenteral nutrition.

FFMI SDS and FMI SDS were not different between children with functional IF or surgical IF and children fully or partially PN-dependent. Boys had a significantly higher FMI SDS (p=0.006) than girls had. Age at time of the body composition measurement was negatively associated with FMI SDS (-0.47, p=0.033). Duration of PN and actual parenteral energy or macronutrient intake were not significantly associated with body composition SDS.

Anthropometry and body composition

At the first BOD POD measurement, a significant correlation was found between WFH SDS and FFMI SDS (0.62, p=0.003) and between BMI SDS and FFMI SDS (0.60, p=0.004). BMI SDS was significantly associated with FMI SDS (0.51, p=0.017).

Table 2. Growth and body composition characteristics

At first body composition measurement	n = 21 n (%)
Weight for age SDS	
Median (IQR)	-0.71 (-1.45 to -0.08)*
SDS < -2	1 (5)
Height for age SDS	
Median (IQR)	-1.55 (-2.15 to -0.89)[b]
SDS < -2	7 (33)
Below TH range	11 (52)
Weight for height SDS	
Median (IQR)	0.28 (-0.32 to 1.08)
SDS < -2	0 (0)
SDS > +2	1 (5)
Body mass index SDS	
Median (IQR)	0.37 (-0.50 to 0.75)
SDS < -2	0 (0)
SDS > +2	1 (5)
MUAC SDS	
Median (IQR)	-0.60 (-1.55 to -0.06)[b]
SDS < -2[a]	4 (19)
Fat mass index SDS (kg/m^2)	
Median (IQR)	0.80 (0.28 to 1.16)[b]
SDS > +2	1 (5)
Fat-free mass index SDS (kg/m^2)	
Median (IQR)	-1.53 (-2.26 to -0.84)[b]
SDS < -2	7 (33)

Legend: [a] MUAC was measured in 20 patients. [b] significantly different from zero.
Abbreviations: IQR, interquartile range; MUAC, mid-upper arm circumference; SDS, standard deviation score; TH, target height.

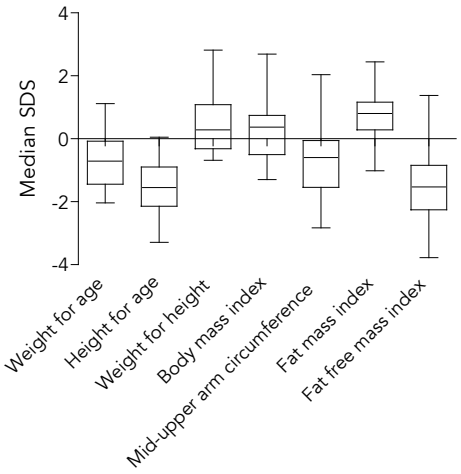

Figure 2. Anthropometric and body composition parameters at baseline, represented as median and ranges (n=21)

Legend: * significantly different from zero.
Abbreviations: SDS, standard deviation scores.

Classification of height measurements and body composition

When looking at the body composition measurements in more detail, several combinations of height parameters and body composition outcomes were possible (**Table 3**). The most commonly found combinations were impaired height with normal FMI and decreased FFMI (n=5) and normal growth with increased FMI and decreased FFMI (n=5).

Table 3. Possible combinations of growth and body composition at first body composition measurement

n* (n=21)	Growth	Fat mass index	Fat-free mass index
5	Impaired	Normal	Decreased
5	Normal	Increased	Decreased
3	Normal	Normal	Decreased
2	Normal	Normal	Normal
2	Impaired	Normal	Normal
2	Impaired	Increased	Increased
1	Impaired	Increased	Normal
1	Impaired	Decreased	Normal

Legend: Impaired growth: growing outside target height range or having a height-for-age <-2 standard deviation. Increased fat mass index or fat-free mass index: >+1 standard deviation, decreased fat mass index or fat-free mass index: <-1 standard deviation.

Longitudinal measurements

A total of 13 patients had repeated body composition measurement after 1 year (**Table 4**). Their baseline growth and body composition SDS were not different from those in patients with only 1 measurement. The median difference in PN dependency between the first and second measurement was 0% (IQR 0 to 4%). Growth and body composition SDS did not change significantly between the first and second measurement.

Table 4. Results of growth and body composition in children with 2 body composition measurements with 1-year interval

Variable	n = 13 n (%) or median (IQR)
Gender: male/female	6/7 (46/54)
Type of IF Surgical/functional	6/7 (46/54)
Time between measurements, years	1.00 (0.96 - 1.07)
Δ Weight-for-age SDS	-0.10 (-0.69 - 0.23)
Δ Height-for-age SDS	-0.14 (-0.33 - 0.13)
Δ Weight-for-height SDS	-0.09 (-0.68 - 0.47)
Δ Body mass index SDS	-0.29 (-0.58 - 0.16)
Δ Mid-upper arm circumference SDS	-0.49 (-1.25 - 0.82)
Δ Fat mass index SDS	0.16 (-0.48 - 0.31)
Δ Fat-free mass index SDS	-0.39 (-0.98 - 0.15)

Legend: Δ, change in growth or body composition SDS between baseline and at 1-year follow-up.
Abbreviations: IF, intestinal failure; IQR, interquartile range; SDS, standard deviation score.

DISCUSSION

This study shows that children with IF have significant body composition abnormalities, with lower FFM and higher FM after correction for their smaller body size. In contrast to their lower weight and height compared with the reference population, their WFH and BMI were not significantly different. To our knowledge, this is the first study to use ADP for the analysis of body composition in children with IF, and it was shown to be feasible. Moreover, this study also prospectively assessed longitudinal body composition changes, showing no significant changes in growth and body composition after 1 year.

Regardless of type of IF and PN dependency, all patients in our study had significantly low FFMI. Low FFM has also been described in previous studies in which most or all children were already weaned off PN.[2,33] In another study using dual-energy X-ray absorptiometry (DEXA) scans, patients had significantly low limb lean mass, especially patients with short bowel syndrome.[3] In addition to low FFM, patients had significantly high FMI. We found that boys had higher FMI than girls had; it is uncertain if this is a real difference or if it reflects the relatively small sample size. No differences in body composition were found between groups classified by type of IF (surgical vs functional) or PN dependency, in contrast to the previous study.[3]

Patients were not only shorter compared with healthy reference children, but half of them were growing below their TH range. This in agreement with a previous study,[2] although in most other studies investigating growth in pediatric IF patients this information is lacking.

In current clinical practice, WFH and BMI are frequently used as a proxy for FM. Strikingly, WFH and BMI of patients with IF were not significantly different from healthy references. This suggests that these frequently used routine parameters are not valid for estimating FM in these children. Indices based on weight and height alone are not sufficient, and body composition should be measured to evaluate FM and FFM. A variety of techniques are available for measuring body composition. This study was the first to use ADP in children with IF and found it to be a feasible method for measuring body composition in this population. **Table 5** summarizes the advantages and disadvantages of ADP compared with DEXA. Compared with other techniques, important advantages of ADP are that it can be used to measure body composition in infants, and it is possible to perform the measurement when the patient has equipment such as a central venous catheter and enterostomy bag in place. However, if not available, other techniques could also be used taking into account their limitations.

This study was the first to prospectively assess longitudinal body composition changes in children with IF. In contrast to the normal population,[34] we found that age at the first

Table 5. Overview of commonly used methods for measuring body composition in children with IF

	ADP	DEXA
Outcome measures	Fat mass Fat-free mass	Fat mas Fat-free mass Bone mineral content
Advantages	No radiation exposure	Whole-body and regional data
	High level of accuracy	Body composition data can be generated together with bone health
	Fast	
	Possible to calibrate devices/central venous line/ additional material	
	Reference values available for infants	
	Possible to measure from birth onwards	
Disadvantages	Expensive device	Radiation exposure
	Only whole-body data	Differences between different scanners
		Very sensitive to subject motion
		Influence of central venous catheter/ enterostomy

Abbreviations: ADP, air displacement plethysmography; DEXA, dual-energy X-ray absorptiometry; IF, intestinal failure.

body composition measurement was negatively associated with FMI, which means that older children tend to have lower FMI than younger children. However, when looking at growth and body composition at baseline and 1 year, we did not find any significant differences.

Abnormal body composition has been observed previously in other chronic diseases such as cystic fibrosis,[35] renal failure,[36] cerebral palsy,[37] and inflammatory bowel disease,[38] but the pathophysiology remains poorly understood. Moreover, comparison with previous studies is difficult because of different ages, methodology, and use of different body composition parameters. The abnormal body composition in patients with IF might be a consequence of excessive energy intake and potential overfeeding when adjustment of PN prescription is based on individual needs taking into account age, activity, and routine growth parameters but not including body composition. In addition, high protein intake has been associated with higher FM in healthy children,[39] but on the other hand, studies have shown that increased protein intake is important for accretion and maintenance of FFM.[40] We did not find any associations between parenteral protein intake and body composition parameters, although the median parenteral amino acid intake (2.0 g/kg/day) was quite high in comparison with the recommended daily parenteral intake of 1.0-2.0 g/kg/day.[15,41] Another factor that might play an important role is decreased physical activity. Although no formal assessment of physical activity was performed and most patients received PN only overnight and were able to participate in usual daily activities including school, clinical experience shows that the group of children with IF may be less

active than healthy children. On the other hand, 1 previous study reporting normal FFM showed similar levels of physical activity compared to healthy controls, using accelerometry.[42] A study in adults with IF showed that 73% had sarcopenia, which includes not only loss of skeletal muscle but also muscle function.[43] Other factors that might influence body composition include prematurity, although results are conflicting,[44-46] and chronic inflammation.[47]

The question of what constitutes optimal growth and how nutrition recommendations should be customized remains. Our results show that body composition abnormalities also occur in children with normal linear growth and children with normal routine weight parameters, so focusing on these standard parameters during follow-up may lead to not recognizing deficiencies in FFM and/or excess in FM. Ideally, in our opinion, nutrition advice should be patient-tailored based on nutrition assessment, taking into account routine growth parameters but also incorporating results from body composition measurement and level of activity. Future intervention studies are needed to create these more customized nutrition recommendations. Currently, patients are advised to participate in normal daily activities as much as possible. However, it might be better to refer them to a physical therapist for a patient-tailored exercise program, for example, including muscle strength improving exercises. The effect of abnormal growth and body composition on long-term outcomes, including neurodevelopment, cardiovascular and metabolic risks, and bone mass development is not well known, and these topics also need to be addressed in future studies.

Our study had some limitations. First, we did not assess physical activity. Ideally, future studies should include assessment of physical activity as well as functional outcome measures, although some of these measures such as hand grip strength are of limited use in young children. Second, we compared body composition values with UK references for BOD POD, since no Dutch reference values are available for ADP. Thirdly, we did not assess the relationship between mucosal inflammation and growth or body composition, although a previous study showed that patients with mucosal inflammation had a higher BMI.[3] Since our patients do not regularly undergo endoscopic evaluation and do not routinely receive corticosteroids, we were not able to investigate this. Fourthly, we were unable to investigate specific associations between body composition and detailed aspects of PN, such as lipid emulsions and micronutrient intake. Future multicenter studies with a larger sample size are needed to give a more tailored advice about the 'best' PN in relation to body composition. Lastly, we did not assess visceral fat or regional fat distribution, although it is thought that visceral fat has more negative effects than subcutaneous fat has.[48]

In conclusion, despite close monitoring of growth and follow-up by a multidisciplinary team, significant abnormalities of body composition were found with significantly lower

FFM and higher FM compared with normal values. This study shows that monitoring of body composition is essential in the treatment of children on long-term PN, especially since children with the same routine growth parameters showed different body composition. Children with IF may benefit from a patient-tailored approach with adjustment of nutrition intake and an advice regarding physical activity based on their body composition to maximize growth and prevent body composition-related problems later in life.

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5

Bone health of children with intestinal failure measured by dual energy X-ray absorptiometry and digital X-ray radiogrammetry

Clin Nutr. 2018 Apr;37(2):687-694.

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ABSTRACT

Background & aims

Children with intestinal failure (IF) receiving long-term parenteral nutrition (PN) are at risk of developing low bone mineral density (BMD). Next to the dual energy X-ray absorptiometry (DXA) method, digital X-ray radiogrammetry (DXR) using the BoneXpert software has become available to obtain the Bone Health Index (BHI) in hand radiographs. In this study we 1) evaluated the prevalence of low BMD in children with IF using DXA and DXR, 2) compared DXA and DXR results, and 3) aimed to identify factors associated with low BMD.

Methods

A retrospective study was performed including all children with IF between 2000 and 2015 who underwent a DXA measurement and/or a hand radiograph. Z-scores of BMD total body (BMD TB) and lumbar spine (BMD LS), bone mineral apparent density (BMAD) and bone health index (BHI) were collected. A low BMD and low BHI were defined as a Z-score ≤-2. DXA and DXR results were compared for cases in which a DXA and hand radiograph were performed within a 6 months' interval.

Results

Forty-six children were included. Overall, 24.3% of the children had a low BMD at the first DXA at a median age of 6 years; correction for growth failure (n=6) reduced this to 16.2%. Fifty percent had a low BHI at the first hand radiograph. Median DXA and BHI Z-scores were significantly lower than reference scores. Age, duration of PN and surgical IF were related to lower Z-scores at the first DXA. Paired DXA and DXR results (n=18) were compared, resulting in a Cohen's kappa of 0.746 ('substantial') for BMD TB. Spearman's correlation coefficient for BHI and BMD TB Z-scores was 0.856 ($p<0.001$). Hand radiography had a sensitivity of 90% and specificity of 86% (BMD TB).

Conclusions

Up to 50% of the children had a low BMD. Children with IF have a significantly poorer bone health than the reference population, also after weaning off PN. Bone health assessment by DXA and DXR showed good agreement, especially for Z-scores ≤-2. DXR assessment using BoneXpert software seems to be feasible for monitoring of bone health in children with IF.

INTRODUCTION

Intestinal failure (IF) in children is defined as a critical reduction of the gut mass or its function below the minimum needed to absorb nutrients required for adequate growth and development. Children with IF depend on parenteral nutrition (PN) for the intake of the required nutrients. In spite of advanced treatment of IF, complications such as bone disease still often occur.[1,2] The cause of bone disease in children with IF seems to be multifactorial. The following factors are thought to contribute: malabsorption or excess loss of calcium and phosphate, vitamin D or K deficiency, chronic intestinal inflammation, medication use (i.e. steroids), PN components (for example aluminum) and the underlying disease itself.[2-4] It has not yet been well established which factors contribute most to IF-associated bone disease.

The prevalence of low bone mineral density (BMD) in children with IF varies between 12.5% and 83%, depending on the definition used and adjustment for delayed growth.[1,2,5] Since more than 90% of the adult bone mass is gained during the first 2 decades of life, low BMD and its consequences may have a great negative impact.[6] Bone health of children with IF is monitored from the age of 4-5 years onwards, the lowest age for which reference data are available for dual-energy X-ray absorptiometry (DXA), the golden standard to assess bone health. However, recently a technique for the evaluation of bone health was introduced for which normative data for Caucasian children above 2 years of age are available. This technique is based on digital X-ray radiogrammetry (DXR) coupled with BoneXpert software (BoneXpert, Version 2, Visiana, Holte, Denmark) in hand radiographs. With this technique, the Bone Health Index (BHI) can be obtained based on the cortical thickness of the three middle metacarpals and the metacarpal width and length of the left hand.[7] Apart from the normative data for younger children, an advantage of DXR is the automated adjustment for actual bone age.

Clinical studies on low BMD in children with IF are scarce, usually cross-sectional and none made use of DXR. In this study we therefore aimed to: 1) evaluate the prevalence of low BMD in children with IF over time; 2) compare DXR and DXA in the assessment of BMD in children with IF; and 3) identify factors associated with low BMD.

MATERIAL AND METHODS

Study population and design

All children followed by our multidisciplinary IF-team between 2000 and 2015 were evaluated. All children who underwent at least one DXA or DXR were included. Children could be dependent on PN or already weaned off. PN was prescribed according to the European Society of Paediatric Gastroenterology, Hepatology and Nutrition and European Society for Clinical Nutrition and Metabolism guidelines (2005), which take into account weight, tolerance and nutritional requirements.[8] Whenever possible, PN was infused overnight, so that the child could participate in daily life activities including school attendance and sports. Micronutrients (i.e. vitamin D and calcium) were supplemented or individually adjusted on the guidance of the measured levels, also in children weaned off PN. Children weaned off PN also visited our multidisciplinary team at least yearly, depending on their age and clinical condition.

We created three groups by the type of IF:

1. SBS, as defined by the Dutch National Working group on SBS in children[9]:
- Resection of ≥ 70% of the small bowel and/or
- Remaining small bowel length measured distal to the ligament of Treitz:
  - Premature: < 50 cm
  - Term neonate: < 75 cm
  - Infant > 1 year: < 100 cm and
- PN needed for > 6 weeks after bowel resection
2. Surgical IF – no SBS:
- Resection of small bowel with remaining small bowel length after resection not as short as covered by the SBS definition above and
- PN needed for > 6 weeks after bowel resection
3. Functional IF:
- Motility disorder/enteropathy with need for PN > 6 weeks. Patients who underwent a bowel resection because of functional IF were also classified in this group on the basis of the primary underlying disease.

In clinical practice, some children dependent on home PN do not fulfill the criteria of a real SBS in terms of cm (or %) of small bowel left. They had for example necrotizing enterocolitis, but only a few centimeters were resected. In these cases, the small bowel length is probably not the problem. We therefore chose to classify these patients as surgical IF – no SBS. Due to the small group sizes of children with motility disorders and

enteropathies and the fact that both disorders lead to long-term PN dependency, we decided to describe them as one group i.e. functional IF.

Data collection

We collected data from birth until January 1, 2015 by reviewing the hospital records. Data included patient characteristics, bowel characteristics, growth characteristics and duration of PN. For the patients in groups 1 and 2, start date of IF was defined as the date of first bowel resection. For patients with functional IF (group 3), the start date of PN was defined as start of IF. Prematurity was defined as a gestational age less than 37 weeks. Z-scores of weight-for-age (WFA), height-for-age (HFA), target height (TH) and weight-for-height (WFH) were calculated using Dutch reference data (2010).[10,11] Patients were considered totally PN dependent when they received 100% of their calories as PN, partially PN dependent when they received less than 100% of their calories as PN. In addition, they were considered weaned off PN when they did not receive PN at the first DXA and did not restart PN afterwards, in contrast to temporary stop when they started again with PN before January 1, 2015.

Assessment of bone health

DXA measurements (GE Lunar Prodigy) were routinely made from the age of 4-5 years, providing measurements of total body (TB) and lumbar spine (LS, L2-L4) BMD (g/cm2). TB and LS BMD Z-scores were determined by comparing the absolute values to national standards, depending on age and sex.[12]

The influence of bone size on measurements of BMD was adjusted using the bone mineral apparent density (BMAD) method. For children with a HFA Z-score < -2 or TH outside the 95% TH range, the BMAD of the lumbar spine was calculated with the following formula[12,13]: BMAD = BMD lumbar spine * [4 / (π * mean width of the second to fourth lumbar vertebral body)]. If growth data were not available for the day of DXA, the data obtained closest to this day were used. Data were noted as a missing value when no measurement had been done within the preceding 6 months.
TH in cm, TH Z-scores and 95% TH range were calculated as follows[14]:

- TH boys = 44.5 + (0.376 * father's height in cm) + (0.411 * mother's height in cm)
- TH girls = 47.1 + (0.334 * father's height in cm) + (0.364 * mother's height in cm)
- TH Z-score boys = (TH in cm – 183.8) / 7.1
- TH Z-score girls = (TH in cm – 170.7) / 6.3
- 95% TH range = TH Z-score ± 1,6 SD

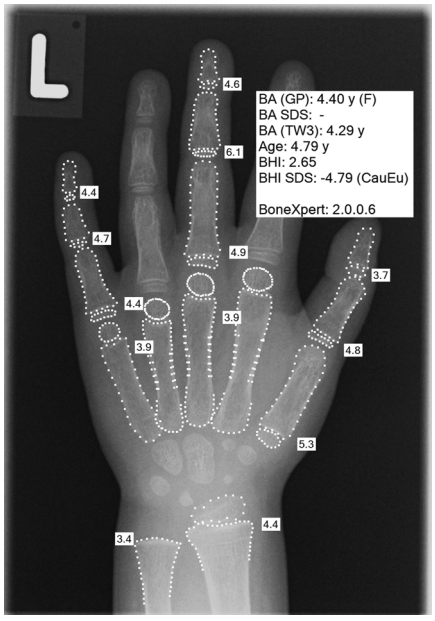
Another method we used to adjust for delayed growth was by calculating the BMD with the height age, defined as the age at which the child's actual height was on the 50th per-

centile (HFA Z-score=0). According to the International Society for Clinical Densitometry, a BMD or BMAD Z-score ≤ -2 was regarded as low.[15]

Next to the use of DXA, bone health was also examined with DXR (**Figure 1**). Standard hand radiographs were taken of the left hand. Bone age was determined based on Greulich-Pyle and the BHI was determined with the BoneXpert software.[7] The formula used is BHI = π x (1 – T/W) / $(LW)^{0.33}$. T is defined as the cortical thickness of the three middle metacarpals, W is the metacarpal width, and L is the bone length. The BoneXpert automatically compares the BHI to a Caucasian reference population with the same sex and converts it to a Z-score adjusted for bone age.[7] Images of hand radiographs made before December 2003 were not available to analyze. Reference values are available for boys above 2.5 years and girls above 2 years of age, and therefore only hand radiographs above this age were analyzed.

The 25-hydroxyvitamin D (25(OH)-vitamin D) concentration in serum was documented, and considered insufficient if < 50 nmol/l. Additionally, the history of fractures was collected.

Figure 1. Example of hand radiograph analyzed with the BoneXpert software



Abbreviations: BA (GP), bone age determined based on Greulich-Pyle; BA SDS, bone age based on Greulich Pyle Z- score; CauEU, Caucasian European patient, BA (TW3), bone age determined based on Tanner-Whitehouse; age, calendar age; BHI, bone health index; BHI SDS, bone health index Z-score.

This study was performed in accordance with the ethical principles of the Declaration of Helsinki. Approval of the local research ethics committee was obtained (MEC-2014-341). Since the retrospective data were analyzed anonymously, a written informed consent was not necessary.

Statistical analysis

Statistical analysis was performed using SPSS Version 21.0 (IBM, Armonk, New York). Categorical variables are summarized as frequency counts and percentages, and continuous variables as mean ± SD when normally distributed or as median and interquartile range (IQR) when not normally distributed. The median duration of PN before the DXA measurement or hand radiograph was calculated with the Kaplan Meier survival curve, since some of the patients were still receiving PN at time of the measurement/radiograph. Differences in continuous variables between the groups were tested using the Mann-Whitney U test for two-groups comparisons, and the Kruskal-Wallis tests for more than two groups. Differences in categorical variables between the groups were tested with the Fisher's exact test. Differences between patients on PN and patients weaned from PN were assessed using the Fisher's exact test and Mann-Whitney U test. To determine whether bone health in the study population differed significantly from that in the reference population, the Wilcoxon one-sample test (compared with zero) was used. To evaluate the change in BMD, the differences between paired measurements (DXA 1 and DXA 2) were calculated and expressed as change per year.

Variables tested for association in univariate regression analysis at the first DXA included sex, age, type of IF, 25(OH)-vitamin D, HFA Z-score (both continuous and dichotomous as Z-score < or ≥ -2), HFA Z-score below TH, WFA and WFH Z-score (both continuous and dichotomous as Z-score < or ≥ -2) and duration of PN. All these variables were included for the multivariate regression analysis with backward elimination (significance level for removal 15%).

To account for the correlations in the repeated measurements of each child we used linear mixed effects models. The fixed-effects part included the covariates duration of PN, presence of PN at measurement, type of IF, interactions between type of IF and duration of PN and the time intervals between the DXA measurements. For the random-effects part random intercepts were included. The optimal random-effects structure was chosen using the AIC criterion, while for the fixed effects p-values were based on t- and F-tests.

DXA and DXR results were compared for cases when the hand radiograph was made within 6 months before or after the DXA. To account for different methodologies, Z-scores were compared. Continuous Z-scores were compared with Cohen's kappa, Spearman correlation coefficient and linear regression.

Statistical significance was set at p-value of 0.05. In case of multiple comparisons, an adjusted significance level was used according to the Bonferroni correction (significance level = 0.05/number of comparisons).

RESULTS

Patient characteristics

Forty-six of the 107 patients followed by our multidisciplinary IF-team between 2000 and 2015 underwent at least one DXA or hand radiograph and were included. Patient characteristics are shown in **Table 1**. The median age at start of IF was 18 days (IQR 3 – 167 days). Twenty-one children (46%) had SBS, 15 children (33%) surgical IF – but no SBS, and 10 children (22%) functional IF. Volvulus was the most common underlying disease, i.e. in 22% of the patients.

DXA results – first DXA

In total, 71 DXA measurements were obtained from 37 patients, with a median of 1 measurement per patient (range 1 - 8 measurements) (**Table 2**). At the first DXA, 76% of the patients were already weaned off PN for a median of 60.1 months (IQR 41.2 – 75.2 months, range 1.3 – 119.1 months). At the first DXA at a median age of 6 years, 24.3% of the children had a low BMD (either BMD TB, LS or BMAD Z-score ≤ -2). Median BMD TB, BMD LS and BMAD Z-scores were significantly lower than the reference population ($p = 0.006$; $p < 0.001$ and $p = 0.004$ respectively). Compared to the reference population, also children weaned off PN at the first DXA had a significantly lower median BMD TB ($p = 0.021$), BMD LS ($p < 0.001$) and BMAD Z-score ($p = 0.012$) than the reference population.

There were no significant differences in BMD Z-scores or BMAD Z-score at the first DXA between the three different groups of IF. Children still receiving PN at the first DXA had a significantly lower median BMD TB Z-score (-1.81, IQR -3.00 to 0.47) than children weaned off PN (-0.34, IQR -1.26 to 0.04, $p = 0.048$). Furthermore, the proportion of patients with a BMD TB Z-score ≤ -2 was significantly higher in the group of patients on PN versus the group of patients weaned off PN ($p = 0.008$).

Factors associated with low BMD

Having an older age at the first DXA was related to lower BMD TB and LS Z-scores at the first DXA ($p = 0.026$ and $p = 0.045$ respectively, in univariate analysis). In addition, having a lower HFA Z-score, a HFA Z-score < -2, a higher WFH Z-score and a longer duration of PN before the first DXA were related to lower BMD LS Z-scores ($p = 0.001$, $p = 0.004$, $p = 0.043$ and $p = 0.044$ respectively).

In a multivariate model that included all variables having an older age at the first DXA and having surgical IF were related to both lower BMD TB and LS Z-scores at the first DXA (**Table 3**). Having a higher WFH Z-score and a longer duration of PN before the first DXA were related to lower BMD LS Z-scores.

At the first DXA or hand radiograph (acceptable time interval ± 6 months), 16 children (33%) had an insufficient 25(OH)-vitamin D. The number of children with an insufficient vitamin D was not significantly different between the group children still on PN and the group children already weaned off. Using univariate or multivariate analysis, this factor was not a significant predictor of BMD Z-scores.

Table 1. Patient characteristics

	N = 46
Gender: male – n (%)	20 (44)
Prematurity (Gestational age < 37 weeks) – n (%)	23 (50)
Age at start of IF (days) – median (IQR)	18 (3 – 167)
HPN – n (%)	29 (63)
Category of IF – n (%)	
SBS	21 (46)
Volvulus	8 (17)
NEC	4 (9)
Intestinal atresia	4 (9)
Gastroschisis	1 (2)
Gastroschisis with atresia	1 (2)
Gastroschisis with volvulus	1 (2)
Ileus	1 (2)
Other	1 (2)
Surgical IF – no SBS	15 (33)
NEC	3 (7)
Intestinal atresia	3 (7)
Volvulus	2 (4)
Ileus	2 (4)
NEC with volvulus	2 (4)
NEC with ileus	1 (2)
Gastroschisis with atresia	1 (2)
Other	1 (2)
Functional	10 (22)
Enteropathy	6 (13)
Motility disorder	4 (9)
Whole small bowel in situ – n (%)	7 (15)
Remaining length small bowel known – n (%)	33 (72)
Remaining length small bowel – median cm (IQR)	50 (31 – 76)
Ileocecal valve in situ – n (%)	27 (59)
Colon in situ – n (%)*	36 (78)
History of enterostomy – n (%)	34 (74)

Legend: *Of which 9 patients without their cecum due to an ileocecal resection.
Abbreviations: HPN, home parenteral nutrition; IF, intestinal failure; NEC, necrotizing enterocolitis; SBS, short bowel syndrome.

Table 2. Demographics and results of bone health assessment of patients analyzed divided into three categories

	Total	SBS	Surgical IF – but no SBS	Functional IF
	n = 46	n = 21 (46%)	n = 15 (33%)	n = 10 (22%)
Gender (male (%))	20 (44)	8 (38)	7 (47)	5 (50)
Age at start of IF – days (IQR)	18 (3 – 167)	7 (2 – 43)*	15 (1 – 49)#	395 (24 – 4419)*#
Patients with ≥ 1 DXA (n (%))	37 (80)	18 (86)	14 (93)	5 (50)
Age at first DXA – years (IQR)	6 (5.5 – 9.9)	6.3 (5.5 – 9.8)	5.7 (5.4 – 7.4)	7.5 (5.3 – 14.3)
PN characteristics at first DXA				
Total PN (n (%))	1 (3)	0 (0)	0 (0)	1 (20)
Partial PN (n (%))	8 (22)	4 (22)	1 (7)	3 (60)
Weaned off PN/temporary stop of PN (n (%))	28 (76)	14 (78)	13 (93)	1 (20)
Time receiving PN before first DXA in months – median (IQR)	9.4 (4.6 – 14.3)	10.2 (1.3 – 19.1)	4.5 (1.3 – 7.8)	67.6**
BMD Z-score total body at first DXA – median (IQR)	-0.53 (-1.38 – 0.03)	-0.45 (-1.29 – 0.02)	-0.56 (-1.56 – -0.05)	-1.26 (-3.00 – 2.67)
BMD Z-score total body ≤ -2 at first DXA (n (%))	5 (14)	1 (6)	2 (14)	2 (40)
BMD Z-score lumbar spine at first DXA – median (IQR)	-0.79 (-1.75 – -0.18)	-0.88 (-1.63 – -0.68)	-0.31 (-1.43 – 0.08)	-1.95 (-3.88 – 1.44)
BMD Z-score lumbar spine ≤ -2 at first DXA (n (%))	6 (16)	3 (17)	1 (7)	2 (40)
BMAD Z-score at first DXA – median (IQR)	-0.53 (-1.32 – 0.28)	-0.80 (-1.66 – 0.06)	-0.32 (-0.96 – 0.44)	-0.65 (-3.00 – 1.59)
BMAD Z-score ≤ -2 at first DXA (n (%))	5 (14)	2 (11)	1 (7)	2 (40)
Patients with ≥ 1 hand radiograph (n (%))	34 (74)	18 (86)	7 (47)	9 (90)
Age at first hand radiograph – years (IQR)	4.6 (3.0 – 7.2)	4.2 (3.0 – 6.4)	5.2 (3.5 – 7.3)	3.9 (2.8 – 12.1)
Difference between calendar age and bone age > 1 year (n (%))	9 (27)	3 (17)	1 (14)	5 (56)
BHI Z-score at first hand radiograph – median (IQR)	-2.24 (-3.60 – -0.66)	-1.48 (-3.50 – 0.06)	-2.66 (-3.17 – -0.85)	-3.13 (-4.29 – -1.31)
BHI Z-score at first hand radiograph ≤ -2 (n (%))	17 (50)	6 (33)	5 (71)	6 (67)

Legend: * Significant difference between SBS and functional IF (p = 0.008), # Significant difference between surgical IF but no SBS and functional IF (p = 0.007). ** Due to the low number of events, no 95% CI is given and differences between groups could not be analyzed.

Abbreviations: BHI, bone health index; BMAD, bone mineral apparent density; BMD, bone mineral density; DXA, dual energy X-ray absorptiometry; IF, intestinal failure; IQR, interquartile range; LS, lumbar spine; PN, parenteral nutrition; SBS, short bowel syndrome; TB, total body.

Table 3. Factors associated with BMD TB and LS Z-scores – results from multivariate analysis

	BMD TB Z-score B-coefficient	p-value	BMD LS Z-score B-coefficient	p-value
Age	-0.185	p = 0.047	-0.253	p < 0.001
Duration of PN	NA	NA	-0.027	p = 0.010
Group of IF (functional)	1.959	p = 0.019	1.534	p = 0.010
WFH Z-score	NS	NS	-0.366	p = 0.033
HFA Z-score	NS	NS	NA	NA
WFA Z-score	NS	NS	NA	NA

Abbreviations: BMD, bone mineral density; HFA, height-for-age; IF, intestinal failure; NA, not applicable, excluded from regression analysis; NS, not significant; LS, lumbar spine; PN, parenteral nutrition; TB, total body; WFA, weight-for-age; WFH, weight-for-height.

Patients with growth failure

At the first DXA, 6/36 children (17%) had growth failure (HFA Z-score < -2). The median BMAD Z-score of these patients was higher (-0.95 (-3.28 - -0.50)) than the BMD LS Z-score (-2.08 (-2.79 - -1.69)). Two out of these 6 children had a BMAD Z-score ≤ -2, in comparison with a BMD LS Z-score ≤ -2 in 3 of these children.

When using the BMAD for children with a height Z-score below their target height range (6/31, 19%), the median BMAD Z-score was -0.68 (-1.32 – 0.65) in comparison with a BMD LS Z-score of -1.89 (-2.03 – -0.29). While 1 of these 6 children had a BMD LS Z-score ≤ -2, none had a BMAD ≤ -2.

When using the height age method for recalculating BMD values, the median corrected BMD TB Z-score was -0.20 (-0.90 – 0.40) versus the uncorrected -0.53 (-1.38 – 0.03). The median corrected BMD LS Z-score was -0.5 (1.1 – 1.5) versus the uncorrected -0.79 (-1.75 – -0.18). The proportion of patients with a BMD Z-score ≤ -2 changed from 5 to 3 (BMD TB) and 6 to 2 (BMD LS) using this correction method. **Table 4** shows the BMD Z-scores at the first DXA, using corrected values for the children with growth failure. Using these values, 16.2% of the children had an abnormal BMD Z-score (either abnormal BMD TB or BMD LS).

Table 4. BMD Z-scores at the first DXA of all children, using corrected values for children with growth failure

	Total group n = 37
BMD Z-score TB, using height age corrected BMD values for children with GF, median (IQR)	-0.37 (-1.29 – 0.03)
BMD Z-score TB ≤ -2, using height age corrected BMD values for children with GF, (n (%))	3 (8)
BMD Z-score LS, using BMAD values for children with growth failure, median (IQR)	-0.71 (-1.43 – -0.18)
BMD Z-score LS ≤ -2, using BMAD values for children with growth failure, (n (%))	5 (14)

Abbreviations: BMD, bone mineral density; DXA, dual energy X-ray absorptiometry; GF, growth failure; LS, lumbar spine.

Longitudinal bone health measurements

Thirteen children had multiple DXA measurements. The median age difference between the first and the second DXA measurement was 2.01 years (1.09 – 2.44 years). The median change in Z-scores per year was +0.16 SD (-0.07 – 0.51) for BMD TB and +0.09 (-0.05 – 0.54) for BMD LS. Using linear mixed models, we did not find any significant predictors of the course of BMD.

Hand radiograph results – first hand radiograph

In total, 66 hand radiographs were obtained from 34 children (Table 2), with a median of 1 hand radiograph per patient (range 1 – 6 hand radiographs). Five hand radiographs (7.6% of all) could not be analyzed due to technical reasons, 1 hand radiograph (1.5%) could not be analyzed because of the very low bone age of this patient. Median BHI Z-score was significantly lower than the reference population ($p < 0.001$). Seventeen children (50%) had a BHI Z-score ≤ -2.

Fractures

In total, 4 children developed multiple fractures, all after minimal trauma, including one child with vertebral compression fractures. The underlying diseases were congenital villous atrophy of unknown origin, jejunal atresia, filamin A mutation with intestinal pseudo-obstruction and microvillus inclusion disease. The age at the first fracture was 5.4 years, 7.7 years, 2.1 years and 1.9 years, respectively. All children were 100% PN dependent at the time of the first fracture. Three patients received bisphosphonates. Two of them had BMD Z-scores TB and/or LS ≤ -2. For the other patient Z-scores were not available because of his young age. The youngest patient did not receive bisphosphonates since her DXA Z-scores were good. None of the patients used enteral or parenteral corticosteroids.

Comparison of DXA and hand radiograph

Z-scores

At a median chronological age of 10.4 (DXA) and 10.1 years (hand radiograph), 24 measurements from 18 patients were paired. Hand radiography (BHI) had a sensitivity of 90% (BMD TB) and 60% (both BMD LS and BMAD) and a specificity of 86% (BMD TB), 79% (BMD LS) and 93% (BMAD) when taking DXA as the reference method (**Tables 5a, 5b and 5c**).

In 16.7% (BMD TB) and 20.8% (BMD LS and BMAD) of the pairs, DXA Z-scores and BHI Z-scores differed > 2 SDS (total of 7 analyzed pairs in 4 patients).

Table 5a. Comparison of classification of bone health according to X-radiograph (BHI) and DXA (BMD total body) in 18 children

	Low BMD TB	Normal BMD TB	Total
Low BHI	9	1	10
Normal BHI	2	12	14
Total	11	13	24

Table 5b. Comparison of classification of bone health according to X-radiograph (BHI) and DXA (BMD lumbar spine) in 18 children

	Low BMD LS	Normal BMD LS	Total
Low BHI	6	4	10
Normal BHI	3	11	14
Total	9	15	24

Table 5c. Comparison of classification of bone health according to X-radiograph (BHI) and DXA (BMAD) in 18 children

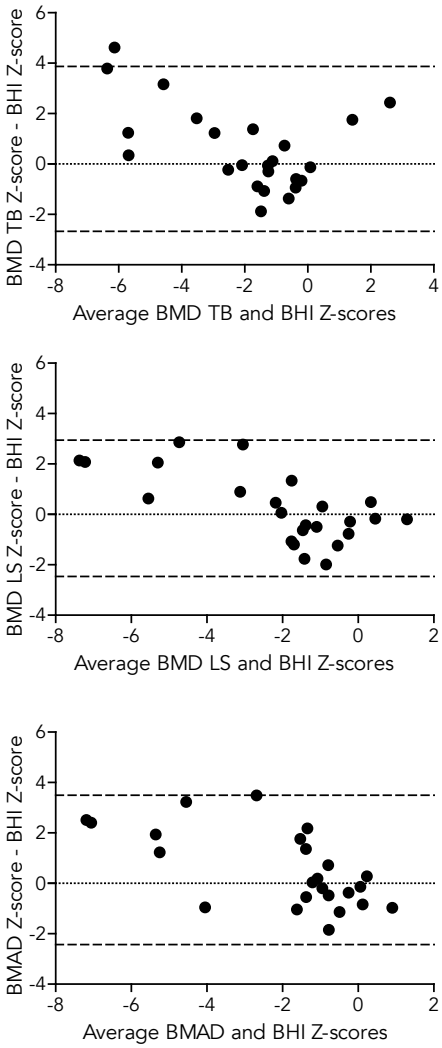
	Low BMAD	Normal BMAD	Total
Low BHI	6	4	10
Normal BHI	1	13	14
Total	7	17	24

Legend: Data are presented as n. Low = Z-score ≤ -2, Normal = Z-score > -2.
Abbreviations: BHI, bone health index; BMAD, bone mineral apparent density; BMD, bone mineral density; DXA, dual energy X-ray absorptiometry; LS, lumbar spine; TB, total body.

Continuous values

Comparison of continuous values of BMD methods yielded Cohen's kappa values of 0.746 (BMD TB, considered substantial), 0.393 (BMD LS, considered fair) and 0.573 (BMAD, considered moderate). There was a significant positive correlation between the BHI Z-score and DXA Z-scores (BMD TB Z-Score; 0.856, $p<0.001$; BMD LS Z-score; 0.799, $p<0.001$ and BMAD Z-score; 0.647, $p=0.001$). **Figure 2** shows the Bland-Altman plots.

Figure 2. Bland Altman plots indicating the differences between DXA (BMD TB, LS and BMAD) and hand radiograph measurements (BHI) for Z-scores



Legend: The horizontal axis shows the mean of the two methods (DXA and DXR) and the vertical axis indicates the difference. The dotted lines represent the 95% limits of agreement.

Abbreviations: BHI, bone health index; BMAD, bone mineral apparent density; BMD, bone mineral density; DXA, dual energy X-ray absorptiometry; LS, lumbar spine; TB, total body.

DISCUSSION

The aim of this study was to assess the prevalence of low BMD in children with IF and to compare two different methods to assess bone health in these children. We also aimed to identify factors influencing the bone health. Our results suggest, firstly, that hand radiography is a feasible alternative method for the assessment of bone health in children with IF. Secondly, we found that up to 50% of the children with IF have a low BMD and that children with IF have a significantly lower BMD than healthy controls. More important, our results show that low BMD is also common after weaning off PN. Thirdly, we found several factors influencing BMD Z-scores at the first DXA, although we could not find any significant predictors of the course of bone health in this retrospective cohort.

To our knowledge, this study is the first comparing DXA and DXR in children with IF. Since hand radiographs are part of the routine growth work-up in children with IF, DXR is an easy method to obtain information about bone health and does not need additional radiation. Other important advantages of DXR include the availability of reference values for young children, direct adjustment for bone age and low costs.[16,17] Correlation coefficients between DXR and DXA were comparable with coefficients found in previous studies in children with growth hormone deficiency and acute leukemia.[18] The Bland Altman plots show that the difference between DXR and DXA tends to be larger when the average of these methods is more negative. Additionally, the variability is not consistent, which is probably due to the relatively small number of measurements. Results for DXR and DXA differed greatly (> 2 Z-scores) in 7 analyzed pairs obtained from 4 patients. In all cases, the BHI Z-score was more negative than the BMD TB Z-score, likely because DXR is more sensitive to deviations than DXA. Additionally, in 5 of these 7 pairs, both the BMD TB Z-score and the BHI Z-score were ≤ -2. Most important for clinical practice, our results show that the agreement between DXR and DXA was good for low BMD (Z-scores ≤ -2), as defined by the International Society for Clinical Densitometry.

Unfortunately, 5 (7.6%) of the hand radiographs could not be analyzed by the BoneXpert software because they were too sharp. This percentage was higher than that in previous studies.[19,20] This could be explained by the fact that those images were not originally intended for BoneXpert analysis. The BoneXpert method is intended to be used on digital radiographs which have not been artificially sharpened by image postprocessing (so called edge enhancement). Since we were unable to recover the original 'raw' images, these images could not be analyzed. In future application of the BoneXpert, it should be ensured that the hand radiographs are not postprocessed excessively.

In this study, the prevalence of low BMD ranged between 14 and 50% depending on the method used (DXA or DXR). A previous study in children with IF reported a prevalence

of low BMD of 83% measured by DXA but used a cut-off BMD Z-score < -1 instead of Z-score ≤ -2.[2] Another study[1] reported a prevalence of low BMD (Z-score ≤ -2) of 42%. The discrepancy in the prevalence of low BMD obtained by DXA measurements may be explained by the different populations studied. The patients in this study by Pichler et al. received PN for a longer period before the first DXA was made (5 years versus 9 months), were older (8 versus 6 years) and commonly had mucosal inflammation and steroid use.[1] Furthermore, most of our patients were weaned off PN at the first DXA. The prevalence we found is comparable with that found by Mutanen et al.[4] This emphasizes the need for continued monitoring of bone health after weaning off PN.

In the present study, the prevalence of children with a low BHI measured by DXR was higher than the prevalence of low BMD measured by DXA. This is probably due to the fact that hand radiographs were performed in children too young for a DXA measurement considered having a high risk of low BMD. Regarding the consequences of low BMD, 4/46 children (8.7%) had multiple fractures, which is lower than previously reported.[1,2,21]

Median BMD and BMAD Z-scores were significantly lower than those in the reference population, not only for patients still receiving PN but also for children already weaned off PN. This is comparable with previous studies.[1,4] BMD Z-scores between the first and second DXA showed a small increase in BMD Z-scores. A previous longitudinal study showed a significant increase in BMD after 1 year in children on PN.[2] Another study, however, reported a mean decrease in BMD Z-scores over 1 and 2 years.[1] These studies are difficult to compare because of different study populations and definitions. In order to be able to compare study results, we propose to use the definition of the International Society for Clinical Densitometry.

Among all the PN and IF-related factors, age and duration of PN had a significant negative influence on the BMD Z-scores of the first DXA. Surgical IF was related to lower Z-scores at the first DXA, in contrast to other studies showing that children with enteropathies and motility disorders had the lowest bone mass.[1,2] Additionally, having a higher WFH Z-score was related to lower Z-scores. This might be explained by the fact that children with a higher WFH Z-score have lower HFA Z-scores (poorer growth), and therefore are inappropriately diagnosed with low BMD because correction for poor growth is not taken into account. In our population, the WFH Z-score was significantly higher in the group of children with a HFA Z-score < -2 ($p = 0.049$, results not shown). 25(OH)-vitamin D levels were not a significant predictor of BMD Z-scores. Using linear mixed models correcting for the correlations in the repeated measurements we did not find any significant predictors of the course of BMD. This may be explained by the relatively small number of repeated measurements in this study.

At the first DXA, around 20% of the children had growth failure or was growing below their TH range. Using the BMAD and height age for these patients reduced the number of children inappropriately diagnosed with low BMD, comparable with the study of Fewtrell et al.[22] Overall, 24.3% of the children had a low BMD at the first DXA without correction for growth failure. Correction reduced this to 16.2%, which might be more realistic. However, BMAD and corrected BMD Z-scores are mainly used for research purposes and not regularly in clinical practice. Additionally, around 25% of the patients had a delayed bone age (difference of > 1 year with calendar age). It would therefore be useful to correct the BMD for bone age in these patients. However, since only 2 of these patients with a delayed bone age had a DXA measurement within 6 months of the hand radiograph, this analysis was not possible.

Some limitations of this study should be addressed. First, as we only included children that underwent a DXA or hand radiograph, there could be a selection bias. Since no strict protocol was followed during the early years of the inclusion period, it is possible that the DXA measurements and hand radiographs were mainly made in children considered at high risk of poor bone health. When we compared these 46 patients to the other 60 patients treated between 2000 and 2015 by our IF team who did not underwent a DXA measurement or hand radiograph, the duration of PN was significantly longer for the described study population (10 months) than for the children that did not underwent a DXA or hand radiograph (6 months). However, the children that did not undergo a DXA measurement or hand radiograph were significantly younger that the children included in our study (median age at January 1, 2015 of 2.9 years versus 9.4 years) and 20 of them were still too young to undergo a DXA measurement or hand radiograph. Prospective studies with monitoring of bone health according to a strict follow-up protocol, will lead to more insights. Second, results of hand radiographs and DXA measurements could not be compared for the younger infants, while the use of the hand radiographs is especially important in this group. Third, because of the retrospective nature of our study, data on associated clinical factors important for bone health, such as vitamin/mineral intake, enteral intake and physical activity could not be systematically collected and therefore not be taken into account. It is, however, part of our practice to give supplements when necessary and nutritional advice at each outpatient visit. Fourth, as our data were collected retrospectively and bone health was measured as part of clinical monitoring, only relatively few repeated measurements were available, restricting longitudinal analysis. Fifth, it was difficult to compare subgroups because of their small sample sizes. Despite these limitations, this longitudinal study still provides novel findings in a representative population of children with IF.

In conclusion, up to 50% of the children with IF in this study were found to have low BMD, even after adjustment for growth failure. Low BMD may have great implications

for gaining peak bone mass and is a risk factor of bone fractures. Close monitoring, prevention and treatment of poor bone health is therefore essential. Since most of these children were already weaned off PN, bone health should be monitored also after weaning. Although further prospective studies need to confirm this, DXR using the BoneXpert software seems to be feasible for monitoring BMD in children with IF, which can be applied from the age of 2.5 years onwards.

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5

Addendum

Treatment of intestinal failure-associated bone fractures with bisphosphonates

ABSTRACT

Background/aims

Children with intestinal failure (IF) are at risk for developing low bone mineral density and osteoporosis. Bisphosphonates can be used for the treatment of osteoporosis. The aim of this study was to describe the effect of bisphosphonates on prevention of IF-associated bone fractures.

Methods

All children treated by the IF team in the Erasmus Medical Center – Sophia Children's Hospital from August 2003 to June 2016 with bone fractures who had received bisphosphonates were included retrospectively.

Results

Out of a total of 55 patients, 3 children with bone fractures who had received bisphosphonates were identified. Underlying diseases were congenital villous atrophy, jejunal atresia and intestinal pseudo-obstruction. Two children developed vertebral compression fractures. With a follow-up between 25 and 132 months after the start of bisphosphonates, new fractures were not seen in 2 of the 3 children. No serious side effects were found.

Conclusion

In our IF population of the last 13 years, 3 children developed bone fractures and received bisphosphonates. After the start of bisphosphonates, no new fractures were seen in 2 of the 3 patients. Future larger, controlled prospective studies are needed to confirm the effect of bisphosphonates on the prevention of IF-associated bone fractures.

INTRODUCTION

Intestinal failure (IF) in children is defined as a critical reduction of the gut mass or its function below the minimum needed to absorb nutrients required for adequate growth and development.[1] Children with IF depend on parenteral nutrition (PN). They are at risk for developing a low bone mineral density (BMD), which seems to be multifactorial.[2,3]

Current monitoring of bone health takes place from the age of 4-5 years onwards, when reference data are available for dualenergy X-ray absorptiometry (DEXA). The prevalence of low BMD in children with IF varies between 13% and 83%, depending on the definition and adjustment for delayed growth.[2,3] Studies have demonstrated that the risk of fractures increases with declining BMD.[4] How often children with IF experience fractures varies between 5% and 24%.[2,3,5] The diagnosis of osteoporosis is made when vertebral compression fractures are present or when the patient has a clinically significant fracture history (≥ 2 long bone fractures by age 10 years or ≥ 3 long bone fractures at any age up to age 19 years) and a BMD SD score (SDS) ≤ -2.0.[6]

Bisphosphonates are used for the treatment of osteoporosis. They inactivate osteoclasts and thereby inhibit bone resorption. One study showed that treatment with bisphosphonates was effective for improving BMD in six children with IF-associated bone disease.[7] None of these children experienced fractures, so it is not well known whether bisphosphonates also have an effect on prevention of IF-associated bone fractures.[7] In this report, we describe 3 children with IF-associated bone fractures and the consequent treatment with bisphosphonates.

MATERIALS AND METHODS

All children with IF who were attending the multidisciplinary IF outpatient clinic in the Erasmus Medical Center – Sophia Children's Hospital from August 2003 to June 2016 who had developed bone fractures were included retrospectively. Our population consisted of 61 children who received home PN (HPN), 6 of them were lost to follow up because of transfer to another IF outpatient clinic.

All fractures were confirmed with x-rays. We collected the BMD SDS obtained with DEXA, based on Dutch reference data.[8] When the height-for-age (HFA) SDS was < -2.0, we calculated the bone mineral apparent density (BMAD).[8] The protocol was to perform DEXA scans from the age of 4-5 years onwards in all children on HPN, and earlier in children with fractures. DEXA scans were repeated every two year when the SDS were normal and yearly when the SDS was < -1. For metatarsal and vertebral compression fractures, we considered the development of multiple fractures at the same moment as one fracture.

PN was described according the European Society for Paediatric Gastroenterology, Hepatology and Nutrition guidelines. We gave bisphosphonates intravenously. Patient 1 received pamidronate in an administration scheme of 3-day infusion every 3 months. This protocol was changed into single-day pamidronate (2 mg/kg) every 3 months for all consecutive patients. All patients received half dose the first time. We collected data from birth until January 10, 2017 by reviewing the medical records.

The local Institutional Review Board of the Erasmus MC in Rotterdam waived the need for consent.

RESULTS

Patient characteristics

Out of the total of 55 patients with IF receiving HPN and treated by our IF team (35 children with PN > 1 year), 3 children with bone fractures who were treated with bisphosphonates were identified. **Table 1** shows the characteristics of these 3 children, whereas **Table 2** displays the DEXA scan results and number of fractures in relation to treatment with bisphosphonates. All fractures were symptomatic.

Table 1. Characteristics of the 3 children with IF and bone fractures

Patient	Sex	Ethnicity	Underlying disease	Age at first fracture years	Duration of PN at first fracture years	Vertebral compression fractures	Other fractures	Age at January 10, 2017 years
1	F	Caucasian	Villous atrophy of unknown origin	5.4	5.0	1: L3 2: Th10-Th12, L1-L2	1: Spiral fracture tibia 2: Distal femur 3: Distal humerus 4: Distal radius (greenstick)	22.5
2	M	Indo-Mediterranean	Jejunal atresia	7.7	7.7	1: Almost all thoracic vertebrae and L1-L4	-	9.9
3	M	Caucasian	Filamin A mutation with intestinal pseudo-obstruction	2.1	1.9	-	1: Distal radius 2: Distal antebrachii 3: Distal femur 4: Proximal radius 5: 4th metatarsal bone 6: Distal fibula 7: 2nd – 5th metatarsal bone	4.7

Abbreviations: IF, intestinal failure; PN, parenteral nutrition.

Patient 1 was born with congenital villous atrophy of unknown origin, for which she started with PN soon after birth. She received PN until the age of 10 years. After that she did tolerate full enteral nutrition. During PN she developed 4 bone fractures and the diagnosis osteoporosis was made. Because of muscle weakness she was walking with a rolling walker. One year after weaning from PN, she developed vertebral compression fractures and started with pamidronate. Her last pamidronate infusion was 9 years ago, after which she did not develop any bone fractures.

Patient 2 is a boy with jejunal atresia and a remaining small bowel length of 65 cm. He was dependent on PN from birth onwards, mainly due to gastrointestinal motility problems. At the age of 7 years, he developed backache. A lateral spinal radiograph showed vertebral compression fractures. Besides the treatment with pamidronate, he wore a brace for a few months. He did not develop any bone fractures after the start of pamidronate.

Table 2. DEXA scans and bone fractures before and after treatment with bisphosphonates

Patient	Age at the start of pamidronate years	Duration of PN at the start of pamidronate years	Height for age at the start of pamidronate SDS	DEXA before pamidronate BMD SDS	DEXA after pamidronate BMD SDS (months after first pamidronate)	Number of pamidronate infusions n (years)	Fractures before pamidronate n (months)	Fractures after start pamidronate n (months)
1	11.55	9.80	-6.12	TB: - 1.7 BMAD LS: not possible	TB: - 4.0 (39) BMAD LS: -5.9 (39)*	4 (1.8)	5 (134)	0 (132)
2	7.93	7.93	-0.03	TB: - 2.7 LS: - 3.3	TB: -1.7 (25) LS: -2.1 (25)	6 (1.6)	1 (25)	0 (25)
3	2.38	2.09	0.05	Not available	TB: Not measured LS: -1.8 (23)	8 (2.1)	2 (95)	5 (29)

Legend: * 2 years after last dose of pamidronate.
Abbreviations: BMAD, bone mineral apparent density; BMD, bone mineral density; DEXA, dual energy X-ray absorptiometry; LS, lumbar spine; PN, parenteral nutrition; TB, total body.

Table 3. Serum concentrations of vitamin D, calcium, phosphate, PTH and ALP and intake of vitamin D, calcium and phosphate before treatment with bisphosphonates

Patient	25-OH vitamin D (mmol/L)	Calcium (mmol/L)	Phosphate (mmol/L)	PTH (pmol/L)	ALP (U/L)	Vitamin D intake (IE/day)	Calcium intake (mmol/kg/day)	Phosphate intake (mmol/kg/day)
1	72	2.11	1.42	11.5*	255	1000 cholecalciferol + 0.3 microgram alphacalcidol orally	Unknown, no PN	Unknown, no PN
2	81	2.40	1.51	5.6	539*	600 (PN) + 1600 cholecalciferol orally	0.2 (PN) + 1000 mg calcium carbonate orally	0.8 (PN)
3	34*	2.32	1.45	22.8*	325	400 (PN)	0.2 (PN)	0.2 (PN)

Legend: *abnormal values. Reference values: 25-OH vitamin D: 50-120 nmol/L, calcium: 2.10-2.60 mmol/L, phosphate: 1.10-1.95 mmol/L (1-3 years) and 1.00-1.80 mmol/L (3-12 years), PTH: 1.4 – 7.3 pmol/L, ALP: <410 U/L (infant), <424 U/L (child).
Abbreviations: ALP, alkaline phosphatase; PN, parenteral nutrition; PTH, parathyroid hormone.

In patient 3, osteoporosis was highly suspected because of the recurrent low impact bone fractures he developed. However, no reference values for BMD are available for his age. Unfortunately, the Bone Health Index could not be determined with the BoneXpert software because of poor image quality of the hand radiograph. As a side effect, hypocalcaemia was found, for which the calcium intake was increased 3-4 times the standard.

Risk factors

Patient 1 and 3 used prophylactic low-molecular weight heparin during treatment with PN to prevent catheter-related thrombosis. No steroids were used. We optimized the amounts

of vitamin D and calcium (both in the PN and enterally) in all children (**Table 3**), after which the serum concentrations normalized. Vitamin K levels were normal in all children. They did not have renal disease. All patients were 100% PN dependent when they developed their first fracture, as they did not tolerate any enteral nutrition except minimal enteral feeding. Aluminum toxicity was not likely because of the use of polyethylene bags. All patients had decreased physical activity when they developed their first fracture; they were less active during daily life and did not do sports. Therefore, we stimulated the performance of weight-bearing exercise. Patients 2 and 3 were still dependent on PN on January 10, 2017.

DISCUSSION

Poor bone health is a serious problem in children with IF.[2,3] Until now, studies mainly reported about the prevalence of low BMD [2,3], and it is not well known if bisphosphonates are effective in preventing future fractures. From the total group of 55 patients receiving HPN, 4 children (7.3%) developed bone fractures. In comparison with previous studies, the percentage of children that developed fractures is low.[2,3,5] The young age of these children illustrates the severity of IF-associated bone disease. Three patients were treated with bisphosphonates. The 4th patient did not receive pamidronate because of good DEXA values. After treatment with bisphosphonates no new fractures were seen in 2 of the 3 patients.

The cause of poor bone health seems to be multifactorial. Factors that may contribute are lack of physical activity, the underlying disease and vitamin D deficiency. All children did not tolerate any enteral nutrition at the time of their first fracture, which suggests that these children might lack some essential nutrients for bone accretion. Furthermore, it is striking that in the present report, all children had a lack of physical activity. The fact that patient 2 regained normal daily activities and therefore had a marked increased physical activity after starting bisphosphonates could have contributed to the fact that he did not develop any further fractures. Regarding the underlying disease, bone disease and fractures have not been described previously in patients with filamin A mutation.[9] Another study did not find an association between the occurrence of fractures and the underlying diagnosis.[10] When comparing the 3 children that received bisphosphonates with the other 33 children on HPN that also underwent DEXA scans, the median BMD SDS for this group at the first DEXA were higher (-0.45 for total body and -0.78 for lumbar spine). Furthermore, vitamin D deficiency was also frequently found in the population of 55 children on HPN.

Early detection and treatment of poor bone health is essential. When children are totally dependent on PN, we advise to make DEXA scans yearly, to be informed about the risk of osteoporosis. Our advice is to perform yearly hand radiographs starting from the age of 2 years to evaluate bone health with the BoneXpert software.[11] With this software it is possible to obtain a Bone Health Index (BHI) SDS. The main advantage of this software is the direct adjustment for bone age and the fact that reference values are available for young children i.e. ≥ 2.5 years of age. Attention should be paid when children with a low BMD present with back pain and a lateral spinal radiograph should be made at low threshold. When the diagnosis osteoporosis is made or highly suspected, children should be referred to a pediatric endocrinologist and bisphosphonates should be considered. A possible side effect of bisphosphonates might be inhibition of growth plate activity and therefore bisphosphonates should be given only when indicated. We give pamidronate

2 mg/kg/day every 3 months for 1 year. After that maintenance for two years may be considered. Moreover, prevention of poor bone health is very important and includes stimulating the performance of weight-bearing exercise, e.g. walking stairs. Calcium and vitamin D intake should be optimized both enterally (if possible) and parenterally.

To the best of our knowledge, we are not aware of any study reporting on children with IF-associated bone fractures who received bisphosphonates. In our IF population of the last 13 years, 4 children with IF developed IF-associated bone fractures, of whom 3 received bisphosphonates without serious side effects. No new fractures were seen in 2 of the 3 patients after the start of bisphosphonates; future larger, controlled prospective studies are needed to confirm a therapeutic effect.

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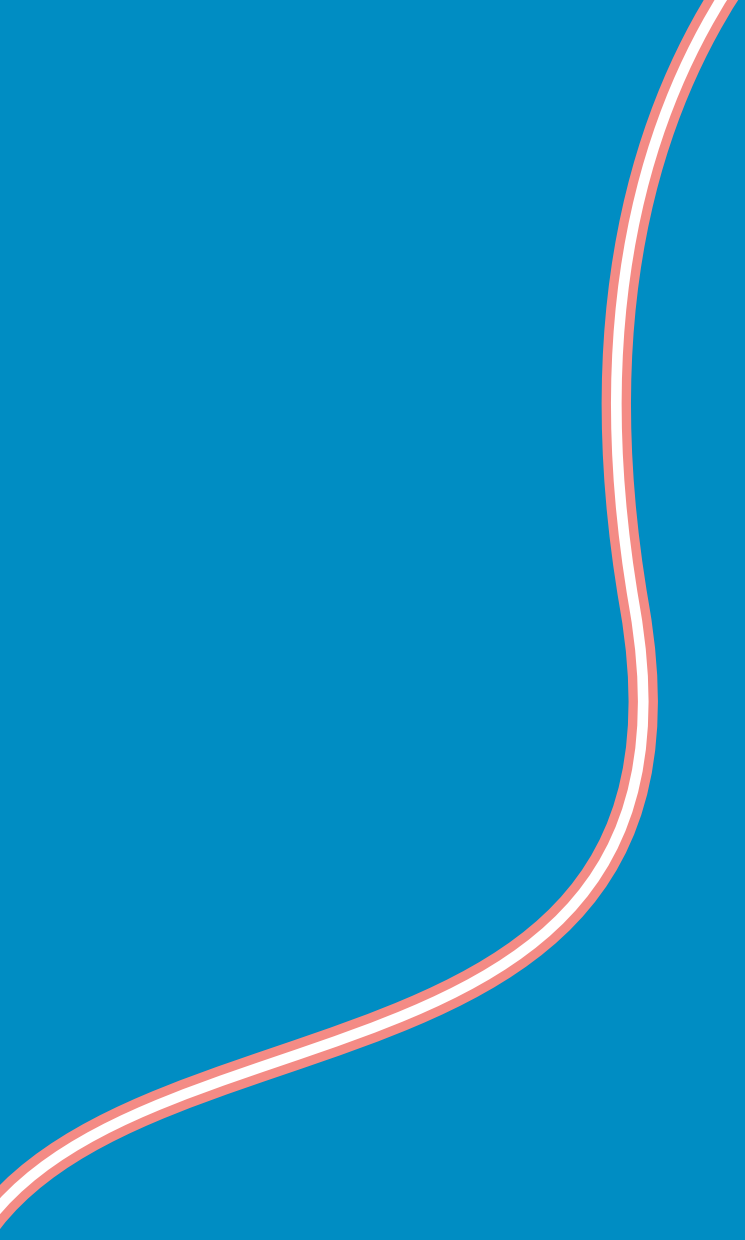

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The gut microbiome in patients with intestinal failure: current evidence and implications for clinical practice

JPEN J Parenter Enteral Nutr. 2019 Feb;43(2):194-205.

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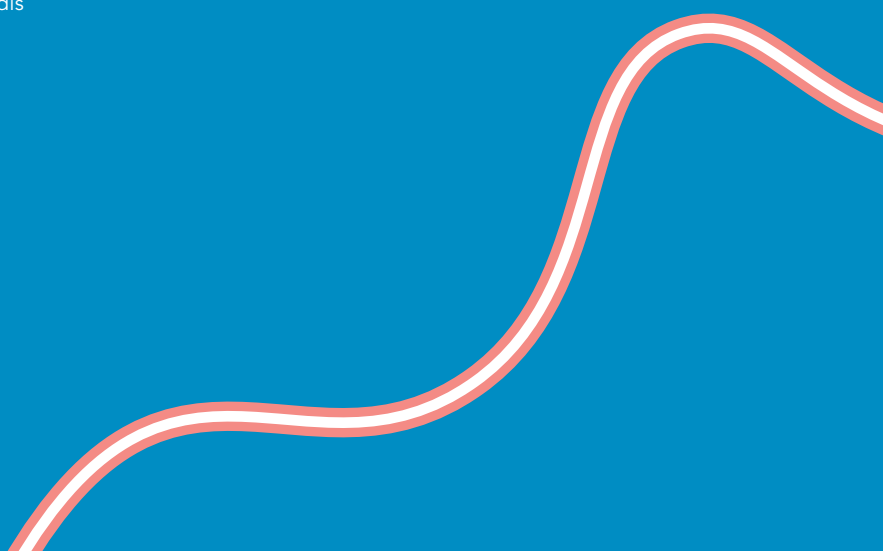


ABSTRACT

Intestinal failure (IF) is the reduction of gut function or mass below a minimum needed to absorb nutrients and fluids, such that patients are dependent on parenteral nutrition (PN). Patients with IF have an altered gut microbiome. Our aim was to review and evaluate the current evidence on gut microbiome and its metabolic activity as well as its association with disease characteristics in adults and children with IF. We performed a PubMed literature search for articles published after 2000 using the following terms: intestinal failure, microbiome, microbiota, short-chain fatty acids, short bowel syndrome and PN. Literature search was restricted to human studies only. The gut microbiome diversity is remarkably reduced, and community structure is altered with a noticeable overabundance of Proteobacteria, especially the Enterobacteriaceae family. A substantial increase in Lactobacillus level is often reported in patients with IF. Gut microbiome characteristics have been associated with poor growth, liver disease, D-lactic acidosis, and duration of intestinal adaptation. Differences in microbiome characteristics have been found between patients receiving PN and those whose guts have adapted and have been weaned off PN. Future research with prospective sample collection should explore the value of the gut microbiome as a biomarker to guide clinical practice and as a modifiable therapeutic target to optimize outcomes of patients with IF.

INTRODUCTION

In the first part of this review, we summarize the primary literature focusing at the gut microbiome characteristics and its association with disease characteristics in patients with intestinal failure (IF). In the second part, we discuss future perspectives on the role of the gut microbiome in the management of patients with IF, including its potential use as a biomarker of intestinal adaptation, prediction of clinical outcomes, and as a therapeutic target.

Intestinal failure

Intestinal failure is defined as the critical reduction of functional gut mass below the minimum needed to absorb nutrients and fluids, such that intravenous supplementation with parenteral nutrition (PN) is required to maintain health and/or growth.[1,2] The intestine is either too short, as a consequence of surgical resection or congenital conditions leading to short bowel syndrome (SBS), or dysfunctional despite adequate length. Symptoms of IF vary from abdominal pain, diarrhea, vomiting, and abdominal distension to dehydration and malnutrition. Patients with SBS may undergo intestinal adaptation, where the remaining small intestine undergoes structural and functional changes to increase its absorptive capacity.[3] This process may eventually allow patients to wean off PN and become fully dependent on enteral and oral feeding.

Human microbiome

It is estimated that the human gastrointestinal tract contains 10^{14} bacteria.[4,5] These gastrointestinal tract-associated microbes are collectively referred to as the gut microbiome. Previous studies have detected bacteria prenatally in the placenta, amniotic fluid, and also in the meconium of newborns.[6-8] Rapid colonization of the gastrointestinal tract starts immediately after birth with its immediate composition depending on gestational age, mode of delivery, and feeding.[9,10] Formula-fed infants tend to have more Bacteroidetes and fewer Actinobacteria and Firmicutes than breast-fed ones.[11]

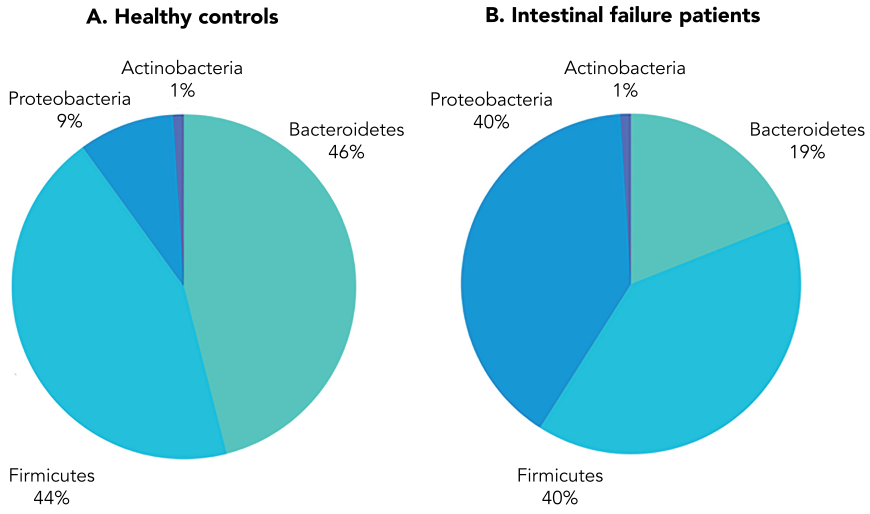
During the first years of life, the gut is gradually colonized, with genetics, environmental factors, diet, and the development of the immune system determining the large extent of compositional variation among individuals.[12-14] The gut microbiome becomes relatively stable in adulthood, with its intraindividual variation being lower than the differences seen between different subjects.[14] Bacteria belonging to Firmicutes and Bacteroidetes phyla dominate the gut and, to a lesser extent, species from Verrucomicrobia, Proteobacteria, and Actinobacteria (**Figure 1**).[15,16]

The gut microbiome is important for several functions such as fermentation and absorption of nutrients in the colon, development of the immune system, and intestinal mucosal

growth and integrity.[17,18] There is growing evidence that certain groups of bacteria such as Clostridia are important for normal intestinal function and protection against intestinal diseases, whereas other proinflammatory bacteria, specifically certain species belonging to Enterobacteriaceae, are harmful.[19-21]

The metabolic functional potential of the microbiome is enormous. Short-chain fatty acids (SCFA) are perhaps the most important bacterial metabolites and end-products of fermentation of nondigestible dietary carbohydrates (i.e. fiber) by anaerobic bacteria. Acetate, propionate and butyrate present 90-95% of the SCFAs produced in the colon.[22,23] Although fiber is the main contributor, proteins, glycoproteins, and peptides from the host's diet and intestinal cell turnover can also constitute fermentation substrate.[24] The colon absorbs >95% of SCFAs[25], contributing to an estimate of 5-10% of the human energy requirements.[26] Moreover, they stimulate vascular flow and motility, increase sodium absorption, affect cell proliferation and differentiation, and promote apoptosis of carcinogenic cells.[22,27,28] Not all bacteria produce the same SCFAs and their molar concentration and proportional ratio in the colon depends also on the type and composition of fermentable carbohydrate.[29]

Figure 1. Pie charts displaying the abundance of major bacterial phyla in patients with intestinal failure and healthy controls



Legend: Average proportions of each phylum were calculated from studies reporting results both in healthy controls and patients with intestinal failure.[30-32] in studies where results are reported in subgroups of patients with intestinal failure, average proportions were calculated first.

METHODS

A PubMed literature search for articles published after 2000 was performed using the following terms: IF, microbiome, microbiota, SCFAs, SBS, and PN. Literature search was restricted to human studies only. References from the selected manuscripts were searched for additional relevant publications. In addition, the literature was evaluated for associations with disease characteristics.

RESULTS

Factors influencing the microbiome in IF

Several factors can influence the gut microbiome in patients with IF (**Figure 2**). Gastrointestinal anatomy and physiology play an important role. Extensive small-bowel resection alters intestinal environment, including luminal pH and oxygen concentration, and enterohepatic circulation of bile acids.[33,34] A study in mice showed that small bowel resection caused Lactobacillus overgrowth, even when not receiving PN.[35] Korpela et al.[36] found that the length of the remaining small bowel was negatively associated with the abundance of *Lactobacillus plantarum* spp. Removal of the ileocecal valve predisposes the small intestine to overgrowth of bacteria, and removal of the ileum may lead to bile acid malabsorption. Bile acids have antimicrobial activity and may lead to a relative abundance of Firmicutes at the expense of Bacteroidetes.[37] The underlying primary disease itself may also be associated with an altered microbiome such as in Crohn's disease.[38-40]

During the phase of intestinal adaptation, oral/enteral nutrition (EN) is initiated as soon as possible to stimulate intestinal function. Factors that may have an effect on the gut microbiome include the type and consequently composition of oral or EN.[9,10] In addition, feeding tubes may act as loci for bacterial attachment and biofilm formation.[41,42] If no EN or oral nutrition is given, this has a substantial impact too. Ralls et al.[43] showed that EN deprivation in patients undergoing small-bowel resection (some receiving PN) led to overabundance of Proteobacteria.

In patients with IF, antibiotics are often used to treat small-intestinal bacterial overgrowth or central line-associated blood stream infections (CLABSI), which can influence the gut microbiome.[44-52] Next to antibiotics, other medications frequently used in IF such as proton pump inhibitors can also alter the gut microbiome.[53]

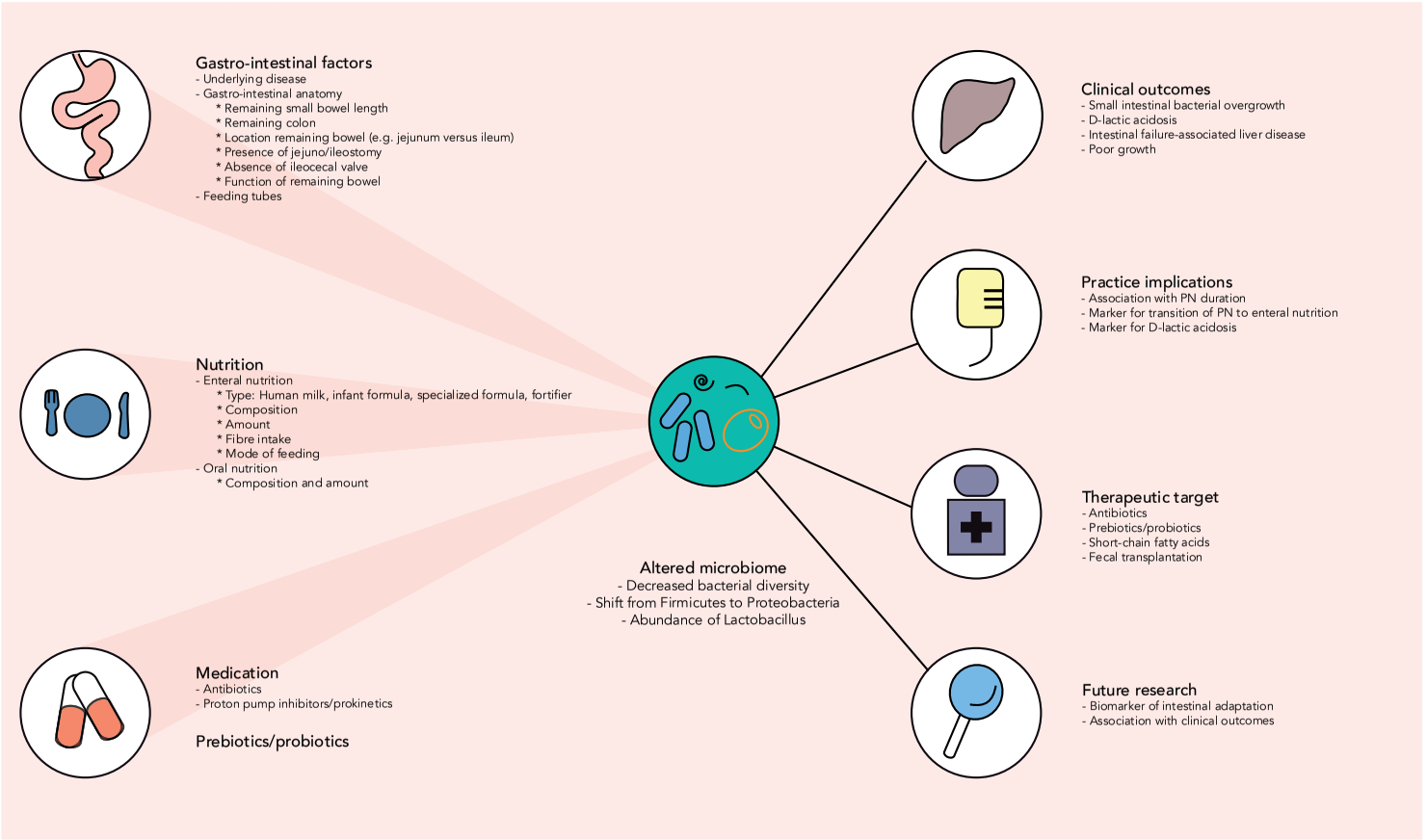
Microbiome in patients with IF

An overview of the results from studies investigating aspects of the gut microbiome in children and adults with IF or SBS is shown in **Table 1 and 2.** The primary aim of these studies was to characterize the gut microbiome composition in these patients. Almost all of these studies used 16S ribosomal RNA (rRNA) gene sequencing on fecal samples.

Alterations in gut microbiome composition

The most consistent finding among studies was an overall reduction in bacterial diversity.[30,32,36,54,55] However, Wang et al.[32] found that the global microbiome diversity, as evaluated by the Shannon index, in infants with SBS without complications [defined as IF associated liver disease (IFALD) or CLABSI] was similar to that of healthy controls.

Figure 2. Factors influencing the gut microbiome in patients with intestinal failure and its implications for clinical practice and future research



Abbreviation: PN, parenteral nutrition.

Table 1. Studies about the gut microbiome in children with intestinal failure

Authors	Participants	Methods	Findings
Korpela et al. 2017	23 children with IF (median age 9.3 years (IQR 4.6-17)) - 17 weaned off PN 58 healthy controls - 3 months old infants (n = 11) - 2 to 6 year old children (n = 35) - Adults (n = 12)	Fecal samples Culture-independent phylogenetic DNA-based microarray analysis	• ↓ diversity and richness • ↑ Lactobacilli, Proteobacteria and Actinobacteria, Clostridium clusters IX, XIII and XV, Fusobacteria, Spirochaetes • ↓ Clostridium clusters III, IV and XIVa • Liver steatosis : ↓ diversity and richness • Patients with steatosis from grade 0 to grade 1: ↑ Proteobacteria, Fusobacteria and low levels of Clostridium • Patients with moderate to severe steatosis (grade 2-3): ↑ Bacilli and Actinobacteria
Wang et al. 2017	18 children with SBS (2-9 months) - All dependent on PN - 14 samples in IFALD group - 5 samples in CLABSI group - 7 samples asymptomatic group 7 healthy controls (4-10 months)	Fecal samples 16S rRNA sequencing Measurement of SCFAs	• ↓ richness in all SBS groups • ↓ diversity in IFALD and CLABSI group compared to asymptomatic SBS patients and healthy controls • IFALD/CLABSI group: ↑ Proteobacteria, ↓ Actinobacteria compared to asymptomatic group • Lower levels of acetate in SBS groups, equal propionate and butyrate and total SCFAs
Piper et al. 2017	8 children with SBS (0.7 – 11.3 years) - 3 weaned off PN - 3 with good growth - 5 with poor growth 3 healthy controls (0.5 – 2.3 years)	Fecal samples 16S rRNA sequencing Metagenomics shotgun sequencing	• ↓ Firmicutes order Clostridiales • Children with SBS and poor growth depletion of Firmicutes, expansion of Enterobacteriaceae • SBS/poor growth: deficient in genes needed for gluconeogenesis, enriched in branched and aromatic amino acid synthesis and citrate cycle pathway genes
Davidovics et al. 2016	9 children with SBS (4 months to 4 years) 8 healthy controls (7-8 years)	Fecal samples 16S rRNA sequencing	• Most dominant phyla Firmicutes, followed by Bacteroidetes, ↑ relative abundance of Proteobacteria and Gammaproteobacteria and Bacilli • Healthy controls ↑ Actinobacteria • Children with SBS and diarrhea ↑ Lactobacillus compared to children without diarrhea
Engstrand Lilja et al. 2015	11 children with IF (1.5 – 7 years) - 6 weaned off PN 7 healthy controls (siblings, 2-13 years)	Fecal samples 16S rRNA sequencing	• ↓ bacterial diversity in children with SBS on PN versus children weaned off PN • Patients with suspected SIBO ↑ Enterobacteriaceae, patient on PN without suspected SIBO ↑ Lactobacillaceae

Legend: Literature published after 2000, case reports excluded.
Abbreviations: CLABSI, central line-associated bloodstream infection; IF, intestinal failure; IFALD, intestinal failure-associated liver disease; PN, parenteral nutrition; SBS, short bowel syndrome; SCFAs, short-chain fatty acids; SIBO, small intestinal bacterial overgrowth.

Table 2. Studies about the gut microbiome in adults with intestinal failure

Authors	Participants	Methods	Findings
Gillard et al. 2017	17 adults with SBS - 9 lactate accumulating, - 7 non-lactate accumulating - 1 with recurrent D-lactic encephalopathy 6 rats with SBS 4 control rats	Fecal samples Real-time quantitative PCR Pyrosequencing Measurement of SCFAs	• Most abundant phyla: Firmicutes, followed by Proteobacteria, Bacteroidetes and Actinobacteria • Lactate accumulating patients: ↓ total SCFAs, ↓ propionate, equal acetate and butyrate • Lactate-accumulating group: ↑ lactate producing bacteria, ↓ lactate-consuming bacteria
Huang et al. 2017	5 adults with type II SBS 5 adults with type III SBS - 2 patients weaned off PN 5 healthy controls	Fecal samples 16S rRNA sequencing	• ↓ diversity • Type II SBS: ↓ Firmicutes and Bacteroidetes, ↑ Proteobacteria compared to healthy controls • Type III SBS: ↑ Bacteroidetes compared to healthy controls • Both type II and III: ↓ Lachnospiraceae, Ruminococcaceae, Peptostreptococcaceae, ↑ Enterococcaceae
Boccia et al. 2017	12 adults with SBS 16 healthy controls	Fecal samples Culture-dependent method Quantitative real-time PCR	• ↓ bacterial counts • ↓ Bacteroidetes, Firmicutes, Bifidobacterium and Methanobrevibacter Smithii
Mayeur et al. 2013	16 adults with type II SBS - 9 lactate accumulating in feces - 7 non-lactate accumulating in feces	Fecal samples Culture analyses and dominant bacterial groups were quantified by real time PCR Measurement of D and L-lactate levels in vitro cultures of bacterial strains and directly in fecal samples	• Predominant bacteria: Lactobacillus/Leuconostoc, ↓ Clostridium and Bacteroidetes • No difference in Lactobacillus between lactate-accumulating and non-lactate accumulating group • Non-accumulator group ↑ Lactobacillus Mucosae
Joly et al. 2010	11 adults with type II SBS 8 healthy controls	Fecal samples and mucosal biopsies Temporal temperature gradient gel electrophoresis Quantitative PCR	• ↓ diversity • High prevalence of Lactobacillus • Poor diversity of Clostridium leptum, Clostridium coccoides and Bacteroidetes • Lactobacillus mucosae detected in patients, not in healthy controls

Legend: Literature published after 2000, case reports excluded. Based on the anatomy of the remaining intestine, SBS is frequently divided into three categories: end-jejunostomy (type 1), jejuno-colic anastomosis where the remnant jejunum is in continuity with part of the colon (type II), and jejuno-ileal anastomosis with ileocecal valve and intact colon in continuity (type III).[2]

Abbreviations: PN, parenteral nutrition; SBS, short bowel syndrome; SCFAs, short-chain fatty acids.

Table 3. Cumulative summary of findings of studies on gut microbiome in patients with intestinal failure

Finding	Studies
↓ **Diversity**	Joly et al. 2010 [54¶] Engstrand Lilja et al. 2015 [55] Huang et al. 2017 [30] Korpela et al. 2017 [36¶] Wang et al. 2017 (in IFALD and CLABSI group) [32]
↓ **Richness**	Huang et al. 2017 [30] Korpela et al. 2017 [36¶] Wang et al. 2017 [32]
↓ **Total bacterial count**	Boccia et al. 2016 [56]
↓ **Number of species**	Wang et al. 2017 (in IFALD and CLABSI group) [32]
↑ **Proteobacteria**	Davidovics et al. 2016 [31] Huang et al. 2017 (in SBS type II patients) [30] Korpela et al. 2017 [36] Wang et al. 2017 (in IFALD and CLABSI group) [32]
↑ Gammaproteobacteria	Davidovics et al. 2016 [31]
↑ Enterobacteriaceae	Engstrand Lilja et al. 2015 [55¶] Piper et al. 2016 [20] Huang et al. 2017 (in SBS type II patients) [30] Wang et al. 2017 (IFALD and CLABSI group) [32¶, †]
↓ **Firmicutes**	Boccia et al. 2016 [56] Piper et al. 2016 [20¶] Huang et al. 2017 (in SBS type II patients) [30]
↑ Bacilli/Lactobacillaceae/Lactobacillus	Joly et al. 2010 [54¶] Mayeur et al. 2013 [57¶,†] Davidovics et al. 2016 [31] Gillard et al. 2017 [58¶,†] Huang et al. 2017 [30] Korpela et al. 2017 [36] Wang et al. 2017 (in IFALD and CLABSI patients) [32†]
Detection of *Lactobacillus mucosae*	Joly et al. 2010 [54¶] Mayeur et al. 2013 [57¶,†]
↑ Enterococcaceae	Huang et al. 2017 [30]
↑ Veillonellaceae	Wang et al. 2017 (in asymptomatic and IFALD patients) [32†]
↑ Clostridium clusters IX, XIII and XV	Korpela et al. 2017 [36]
↓ Clostridium clusters III, IV, XIVa bacteria	Korpela et al. 2017 [36]
↓ Clostridiales	Piper et al. 2016 [20]
↓ *Clostridium leptum, Clostridium coccoides*	Joly et al. 2010 [54¶]
↓ Lachnospiraceae	Huang et al. 2017 [30]
↓ Ruminococcaceae	Huang et al. 2017 [30]
↓ Peptostreptococcacae	Huang et al. 2017 [30]
↓ Erysipelotrichaceae	Huang et al. 2017 [30]
↓ **Bacteroidetes**	Joly et al. 2010 [54] Boccia et al. 2016 [56] Huang et al. 2017 (in SBS type II patients) [30] Wang et al. 2017 [32†]
↑ **Bacteroidetes**	Huang et al. 2017 (in SBS type III patients) [30]
↓ **Actinobacteria**	Davidovics et al. 2016 [31]

Table 3. Cumulative summary of findings of studies on gut microbiome in patients with intestinal failure (continued)

Finding	Studies
↑ **Actinobacteria**	Korpela et al. 2017 [36]
↓ Bifidobacterium	Boccia et al. 2016 [56]
↓ *Methanobrevibacter Smithii*	Boccia et al. 2016 [56]
↑ **Fusobacteria**	Korpela et al. 2017 [36]

Legend: Richness: Number of different species represented in gut microbiome; Diversity: A metric of species richness and their species evenness (i.e. how close in numbers each species is in a community). Based on the anatomy of the remaining intestine, SBS is frequently divided into three categories: end-jejunostomy (type 1), jejuno-colic anastomosis where the remnant jejunum is in continuity with part of the colon (type II), and jejuno-ileal anastomosis with ileocecal valve and intact colon in continuity (type III).[2] Only differences are reported. ¶ No p-values mentioned. † No comparison with healthy controls.
Abbreviations: CLABSI, central line-associated bloodstream infection; IFALD, intestinal failure-associated liver disease; SBS, short bowel syndrome..

Apart from a reduction in bacterial diversity, several studies also reported a reduction in bacterial richness, with the number of species representing the gut microbial community.[32,36] The results of studies in children are in accordance with those in adults.

Looking at compositional changes, most studies found a striking increase of gram-negative Proteobacteria, especially Gammaproteobacteria and their family Enterobacteriaceae (**Figure 1, Table 3**).[20,30-32,36,55] In healthy people, Proteobacteria represent a very small proportion of the intestinal microbiome (1-2%), but in patients with IF these species become a dominant member of the community. The overabundance of Proteobacteria during treatment with PN may be caused by lack of dietary fermentable substrate, such as fiber and resistance starch, in the gut lumen, necessary for growth of certain dominant species. This "gut starvation" effect and lack of interspecies competition offers the opportunity for subdominant species in the microbial community to increase over its dominant members.

In addition, a depletion of Bacteroidetes was found[30,32,54,56], and patients with IF presented low levels of Firmicutes of the order Clostridiales.[20,36,54] Another prominent difference from healthy controls is the overabundance of Bacilli, mainly Lactobacillus.[30-32,36,54,55,57,58] The increase in Lactobacillus is an important difference because in healthy subjects this group contributes <1% to the gut microbiome. The clinical significance of the increase in Lactobacillus remains unknown. One study reported that dominance of *Lactobacillus plantarum* spp. was associated with a relatively long PN duration before the possibility to wean off PN (i.e. successful intestinal adaptation)[36], whereas another study reported that this was associated with shorter PN duration.[30] In addition, depletion of Lactobacillus was associated with poor growth.[20] Other studies found that high levels of Lactobacillus were associated with diarrhea[31] and certain strains may cause D-lactic acidosis.[57] Certain strains like *Lactobacillus mucosae* were found in adults with SBS while this species has hardly ever been described in healthy humans.[54,57]

Alterations in microbiome functionality

Little is known about the metabolic activity of the gut microbiome of patients with IF. A previous study in children with IF showed that the fecal concentration of acetate was lower in children with IF compared to healthy controls, whereas there was no difference in propionate, butyrate, and total SCFA levels.[32]

In adults with a jejunocolic anastomosis, the abundance of *Clostridium leptum* and *Clostridium coccoides*, main butyrate-producing bacteria[59], was low.[54,57] Other studies also found low levels of butyrate-producing bacteria in patients with IF[36,58] or low levels of Firmicutes, known as major fiber fermenters.[20,30,56] Deficiency or depletion of these bacteria may affect the concentration of butyrate, an SCFA with established anti-inflammatory properties, and a major energy substrate for the intestinal epithelium of the colon.[60,61] However, in the aforementioned study, butyrate levels were not different in children with IF compared with healthy children.[32] A possible explanation for this might be that there is increased cross-feeding between acetate-producing and acetate-utilizing bacteria[62], hence acetate is used to produce butyrate[61], although more evidence is needed to confirm these findings.

The only study that used shotgun metagenomics sequencing found differences in carbohydrate metabolizing genes between patients with SBS and healthy control subjects. The gut microbiome of children with SBS was deficient in genes needed for gluconeogenesis but enriched in branched and aromatic amino acid synthesis and citrate cycle pathways.[20]

In addition to limitations pertinent to the laboratory methodologies used, there are also limitations due to the lack of clinical metadata potentially affecting microbiome characteristics and a scarcity of published data exploring clinically important associations. For example, information about the amount and type of EN/oral nutrition was often not reported. Because IF is a rare disease, most of the studies had small sample sizes and heterogeneous population characteristics. Most studies were of cross-sectional design, and prospective studies assessing the microbial changes in patients with IF during the process of intestinal adaptation are lacking. Therefore, there is a need for large, international, multicenter studies where successive data and samples will be collected prospectively from diagnosis and throughout the course of the disease.

Difference between patients on PN versus patients who have successfully weaned off

Patients with successful intestinal adaptation are able to stop PN; therefore, it is of interest to know if their gut microbiome is different compared to patients unable to wean off of PN and healthy control subjects. This is particularly important to explore because it may offer an opportunity to use gut microbiome characteristics as prognostic

biomarkers of intestinal adaptation or potentially manipulate gut microbial colonization with therapeutic interventions.

Although it was not the primary objective of the current literature, some authors described differences of the gut microbiome between patients with IF receiving PN and patients weaned off of PN. Engstrand Lilja et al.[55] found that microbiome diversity was significantly reduced in children with SBS receiving PN compared to children weaned off of PN. However, the diversity in children weaned off was still lower than that of healthy control subjects. They also found that children receiving PN had a higher relative abundance of Enterobacteriaceae than children weaned off of PN and control subjects. This is in line with the study of Korpela et al.[36], showing that most patients with a high abundance of Proteobacteria were still receiving PN and had received PN for a prolonged duration, whereas most patients with a high abundance of Clostridium cluster XIVa had weaned off of PN several years earlier and had been receiving PN for a limited time. Also Huang et al.[30] showed that Enterobacteriaceae was correlated with a longer PN duration, whereas predominance of Lactobacillus was associated with a shorter PN duration. In contrast, Piper et al.[20] found that there was no significant difference in potentially proinflammatory bacteria belonging to Enterobacteriaceae between children receiving PN versus children weaned off of PN.

These early data suggest that patients with IF able to wean off of PN have a gut microbiome more similar to healthy control subjects than patients who are unable to stop PN. However, analysis comparing patient characteristics between children weaned off of PN vs children not able to wean off were not performed, probably due to the small sample sizes and high heterogeneity. Differences in the gut microbiome could also be due to reverse causality and availability of luminal nutrients for bacterial growth from initiation of EN/oral nutrition. In the current literature, the duration of time that the patients had been weaned off of PN was often not known, and it is unknown if their diet was comparable to healthy control subjects.

Gut microbiome in IF and clinical outcomes

D-lactic acidosis

Small-intestinal bacterial overgrowth is a common complication in patients with IF that has direct impact on morbidity and mortality[63,64], and has been associated with dependence on PN.[65] Overgrowth of gram-positive anaerobes in the colon such as Lactobacilli, as well as poor metabolism of D-lactic acid and transfer in circulation can cause D-lactic acidosis. This is an unusual form of lactic acidosis in patients with SBS that may lead to neurological symptoms.[66-68] Treatment includes antibiotics, correction of metabolic acidosis, and restricting oral/enteral intake of carbohydrates.[69,70] Recently, a case report

has been published in which a 15-year-old patient with SBS suffering from recurrent D-lactic acidosis was successfully treated with fecal transplantation.[71]

Intestinal failure-associated liver disease

Many factors have been implicated in the development of intestinal failure-associated liver disease (IFALD).[72-74] Recent studies suggest that decrease in microbial diversity and overgrowth of certain bacterial groups are associated with IFALD. Korpela et al.[36] showed that increased abundance of Proteobacteria was strongly associated with liver steatosis, portal and intestinal inflammation, and liver fibrosis. The effect of the gut microbiome on liver steatosis in patients with IF was more predictive than the duration of PN or length of the residual intestine. Wang et al.[32] also showed that overrepresentation of Proteobacteria was common in children with IFALD. Many species belonging to Proteobacteria are opportunistic pathogens, such as *Escherichia coli*. A possible mechanism by which Proteobacteria may induce liver injury is via gut-derived lipopolysaccharide (LPS). LPS is a potent hepatotoxic inflammatory compound originating from gram-negative bacteria in the gut microbiota, including Proteobacteria. It normally penetrates the intestinal mucosa in trace amounts, enters the portal circulation, and becomes cleared in the liver. LPS has been involved in the pathogenesis of non-alcoholic fatty liver disease, leading to activation of toll-like receptors, promoting inflammation and fibrogenesis.[75,76] It is therefore possible that the increased abundance on Proteobacteria in patients with IF in conjunction with a compromised intestinal barrier function expose liver to higher, than normal concentrations of LPS.[77-79] Another group of bacteria that may cause liver damage are species belonging to Lactobacillus that may promote liver steatosis via excessive bile acid deconjugation.[36]

Poor growth

Piper et al.[20] showed that, from a small number of participants, children with SBS and poor growth (defined as decline in their weight z-score) had a depletion of the bacterial phylum Firmicutes compared with patients with SBS and good growth. However, the causal direction of this association is difficult to establish. It is possible that Firmicutes can harvest energy from fermentation of indigestible or malabsorbed nutrients and make it indirectly available to the host.[80] It is, however, equally possible that gut starvation from PN can deplete species that are dependent on the host's diet, such as Firmicutes, although the energy intake did not differ between children with poor vs good growth.

DISCUSSION

The microbiome as a biomarker of disease management in patients with IF

To date, there are no guidelines on the optimal timing for transition from PN to EN and there is not an ideal marker to use at present.[3] In the case of IF patients on PN treatment, changes in the gut microbiome during gut adaptation may potentially be used as biomarkers to judge the optimal time of transition from PN to EN. Prospective studies are required to assess longitudinal changes of the microbiome and their metabolic products in patients with IF undergoing gradual gut adaptation. The biomarker of choice to use in routine clinical practice should be quick to measure and the costs should be low. Current, yet limited, evidence suggests that SCFAs are altered in patients with IF. Considering their dependency on host diet and speed and the low cost of measuring them, they may fulfil the criteria of a biomarker to dictate the timing of introduction and advancement of EN. This hypothesis needs to be confirmed formally in well-designed prospective studies.

Next to the use of the gut microbiome as a biomarker for intestinal adaptation and advancement of EN, the microbiome might also be used to screen for risk for D-lactic acidosis. Mayeur et al.[57] suggest that the D/L fecal lactate ratio seems to be a proxy index for changes in the microbiome of patients with SBS and might be used to detect patients at risk for D-lactic acidosis. In a more recent study, they reported that patients accumulating lactate in their feces had more lactate-producing bacteria and a lower proportion of lactate-consuming bacteria, suggesting that the microbiome could be used to detect patients at risk of accumulation of lactate.[58]

Microbial therapeutic interventions in IF

The dysbiotic IF microbiome may be a therapeutic target for modulation. Potent interventions to manipulate the gut microbiome include the use of pharmacological doses of SCFAs, prebiotics, probiotics, antibiotics, and fecal transplantation.

Because SCFAs promote cell proliferation and differentiation of colonocytes, prevent growth of opportunistic pathogens and are key regulators of immune response [22,28] it might be beneficial to use SCFAs as a trophic factor to stimulate and promote intestinal adaptation. Previous studies in animals showed that supplementation of PN solutions with butyrate or mixed SCFAs may enhance intestinal adaptation[81-84], an effect which is mediated by upregulation of glucagon like petide-2 (GLP-2)[85], an intestinal trophic peptide. However, the role of SCFAs in this process is not always well established. In necrotizing enterocolitis, increased concentration of butyrate was associated with impaired barrier function, whereas in low levels it seemed to be of benefit to the host.[86]

Beyond the use of SCFAs, a study in piglets showed that intestinal adaptation was stimulated by prebiotic or synbiotic supplementation.[87] Limited evidence suggests that synbiotics may increase fecal SCFA levels and fecal levels of Bifidobacteria, total facultative anaerobic bacteria, Enterobacteriaceae, and Lactobacilli.[88] In a case report of a patient with SBS and recurrent episodes of neurologic dysfunction due to D-lactic acidosis, treatment with synbiotics was associated with a decline in D-lactate and the patient was free of recurrent episodes for 3 years without dietary restriction.[89] However, cases of bacteremia with prescribed probiotic bacteria in infants with SBS have also been reported.[90] Treatment with *Lactobacillus rhamnosus* had no effects on intestinal permeability, and was associated with a positive breath hydrogen test in a single patient.[91] Because the efficacy of probiotics in patients with SBS has not yet been adequately assessed, routine use of probiotics is currently not recommended in clinical practice.[92] The effect of fiber or prebiotic supplementation has not been explored in patients with IF on PN and might not be indicated in patients at risk of bacterial overgrowth.

Fecal transplantation has been first developed for the treatment of patients with chronic *Clostridium difficile* infection after failure to respond to antibiotic therapy.[93] Recently, a child with SBS and recurrent, therapy-resistant, D-lactic acidosis was successfully treated with fecal transplantation.[71] Fecal transplantation could therefore be a treatment alternative in selected patients with IF/SBS with dysbiosis who are at risk of D-lactic acidosis. However, risks associated with fecal transplantation such as bacterial translocation and septic shock are currently unknown, as well as the duration of the effect.

CONCLUSION

Patients with IF have an altered gut microbiome and altered metabolic activity. Although the amount of literature is small, the current evidence is remarkably consistent. Despite differences in the primary pathology and underlying disease the effect of IF on gut microbiome is very similar with profound shifts with an increase of Proteobacteria, especially Enterobacteriaceae, and a decrease of Bacteroidetes and often Firmicutes. Bacterial diversity is remarkably decreased, and there is high abundance of Lactobacillus. The changes found in children are in accordance with those in adults. Differences in microbiome characteristics have been found between patients receiving PN and those whose guts have adapted and have been weaned off of PN. There is potential to use the gut microbiome as a biomarker to guide clinical practice during intestinal adaptation as well as a modifiable therapeutic target.

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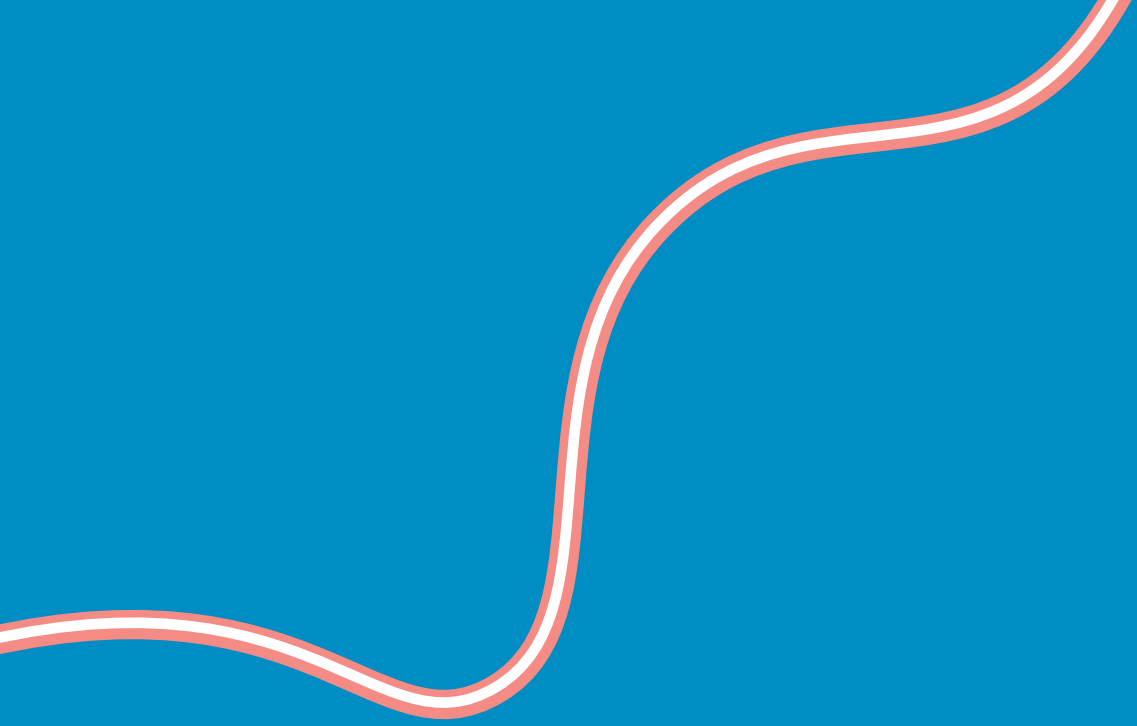

7

Gut microbiota and its metabolic activity in children with intestinal failure dependent on long-term parenteral nutrition

In preparation

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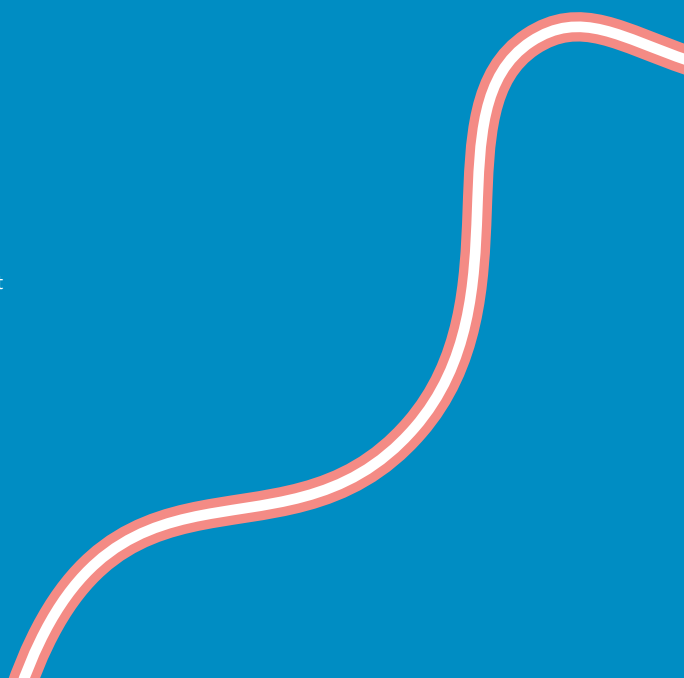


ABSTRACT

Introduction

This study aimed to characterise the gut microbiota composition and its metabolic activity in children with intestinal failure (IF) compared with healthy controls in a longitudinal way and to explore associations with clinical parameters.

Methods

Clinical data and serial fecal samples (n=68) were collected from 15 IF patients (median age 4.3y, dependent on parenteral nutrition (PN) for a median of 3.6y) and single control samples from 25 healthy children. The median time between the first and last sample of each patient was 14 months (IQR 10-21). Fecal microbiota using 16S rRNA gene amplicon sequencing, short-chain fatty acids (SCFA), branched-chain fatty acids (BCFA), D and L isomers of lactate, were measured.

Results

At the first sample, IF patients had lower concentration of total SCFA ($p=0.008$), propionic acid and butyric acid ($p<0.001$) and a higher concentration of D- and L-lactate than healthy controls ($p<0.001$). Patients had a lower total bacterial load (16S rRNA gene copies/g, $p=0.003$); their microbial community was characterised by a lower α-diversity (Shannon index) and evenness (metric of species distribution, both $p<0.001$) and taxon richness (number of distinct species, $p=0.006$) than healthy controls. Patients with surgical IF had lower α-diversity ($p<0.039$) than patients with functional IF. When looking at all samples, the percentage of calories provided by PN (%PN) was negatively associated with microbial diversity. Duration of PN, %PN and fiber intake explained most of the variation in microbial community structure (respectively 6, 6 and 5%). At family level, patients had a significantly higher abundance of Enterobacteriaceae and Staphylococcaceae, and lower abundance of Bacteroidaceae and Bifidobacteriaceae. Two patients weaned off PN; after weaning their microbial structure moved closer to that of the healthy controls.

Conclusions

The microbiota of paediatric IF patients is distinct to that of healthy controls with altered production of SCFA/BCFA, lower bacterial diversity than healthy controls, loss of dominant microbial taxa and increased abundance of sub-dominant and potentially harmful species. Associations between microbial characteristics and clinical parameters associated with PN offer the potential to use the gut microbiota as a biomarker to guide clinical practice during intestinal adaptation.

INTRODUCTION

Patients with intestinal failure (IF) cannot absorb enough nutrients and fluids[1,2] because of a critical reduction of functional gut mass and are therefore dependent on parenteral nutrition (PN). The intestine is either too short, as a consequence of surgical resection or congenital conditions, or dysfunctional despite adequate length.

The gut microbiota plays a key role in fermentation and absorption of nutrients.[3,4] Previous studies have reported an altered gut microbiota composition in patients with IF, including a marked decrease in bacterial diversity[5-7] and an increase in the relative abundance of pathogenic bacteria.[5-10] These compositional shifts in the gut microbiota together with changes in luminal availability of the amount and type of nutrients are likely to influence microbiota metabolism and luminal microenvironment with subsequent consequences to the host. As a result, the metabolism of short-chain fatty acids (SCFA) may change. These are important end-products of fermentation of non-digestible dietary carbohydrates, indirectly contributing to energy for the host, stimulating vascular flow and motility, cell proliferation, differentiation and apoptosis of carcinogenic cells.[11-13] A previous study in children with IF showed that fecal concentration of SCFA acetate was lower in children with IF compared to healthy controls, while there was no difference in propionate, butyrate and total SCFA levels.[7]

Gut microbiota in the light of IF has been associated with adverse clinical outcomes such as bacterial translocation, onset of D-lactic acidosis, central-line associated bloodstream infection, poor growth, and liver disease.[6,7,10] However, most of the previous literature is based on cross-sectional data. In addition, most studies have focused on children with short bowel syndrome; only one study has included children with functional IF.[6] It would be of interest to compare the microbiota between functional IF patients and surgical IF patients, since they have different gastro-intestinal anatomy. Moreover, most functional IF patients are not expected to wean off PN, whereas surgical IF patients might be able to wean off because of the process of intestinal adaptation.

The aim of this study was to prospectively characterise the fecal microbiota of children with IF over time, including the measurement of SCFA, calprotectin and secretory IgA, and relate it with clinical characteristics.

METHODS

Study population

Children stable on home PN (> 3 months) attending the IF team of the Erasmus Medical Center – Sophia Children's Hospital were asked to participate in a prospective observational study. Additionally, 25 otherwise healthy Dutch children were recruited through word of mouth. None of them had undergone previous gastro-intestinal surgery and none of them had received antibiotics for at least two months prior to fecal sample collection. The study was approved by the local research ethical committees (MEC 2015-002, Dutch Trial Register NTR6080) and informed consent of the patients, healthy controls and/or their parents was obtained.

Clinical data

Demographic and clinical data (e.g. underlying disease, duration of PN) were obtained from the medical records. Height and body mass index (BMI) standard deviation score (SDS) were calculated using the latest available Dutch national reference standards.[14] Target height and target height range (±1.6 SDS) were calculated as described previously.[14-16] Percentage PN was used as a measure of PN dependency and was defined as the percentage of total energy intake provided by PN. In addition, we calculated the calories of PN provided, divided by the resting energy expenditure (REE), as calculated by the Schofield formula.[17] Oral nutrition was defined as a normal diet appropriate for age. Patients were considered to suffer from small intestinal bacterial overgrowth if they had associated symptoms (e.g. bloating, abdominal distension, diarrhea) requiring use of antibiotics.

Fecal sample collection

Fecal samples were collected directly from the diaper, the enterostomy, or using a 'feces hat' placed in the toilet and immediately transferred into a sterile tube. We collected samples longitudinally during 2 years, aiming at collecting samples every 3 months if patients were visiting the outpatient clinic. A single fecal sample was collected from the 25 healthy controls.

For microbiota analysis, samples were stored at -80°C and DNA was extracted within a maximum of 2 months of sample collection. For SCFA, fecal samples were homogenized in NaOH 1M w/v and stored at -20°C until analysis. Fecal water content was calculated after lyophilization of the samples.

Calprotectin

Fecal calprotectin concentration, a proxy marker of colonic inflammation, was measured with the Bühlmann ELISA, with normal values of 5-50 µg/g.[18]

Secretory IgA

Secretory IgA in feces was measured with the IDK® sIgA kit (K8870, Immundiagnostik, Bensheim, Germany) and according to the manufacturer specifications, with reported normal values of 510-2040 µg/ml.

Fecal lactate

D and L isomers of lactate were measured in freeze-dried fecal samples using an enzymatic commercial assay (D-lactic acid and L-lactic acid, Boehringer Mannheim Roche) scaled down for use to a 96 microtiter plate (see supplementary methods).

Short-chain and branched-chain fatty acids

Short-chain fatty acids (SCFA; C2-C8) and branched-chain fatty acids (BCFA; iC4-iC6) were measured by gas chromatography (see supplementary methods).[19] Results were presented per gram dry mass of fecal material (µmol/g) and as proportional ratio (%) to total SCFA.

Microbiota

The composition of the gut microbiota was characterised with amplicon sequencing of the V4 region of the 16S rRNA gene. Bacterial DNA was isolated using the bead-beating combined with the chaotropic method.[19,20] The concentration, purity and integrity of DNA were estimated visually by electrophoresis on 1% agarose gel and using Nanodrop™ and Qubit™. Quantification of total bacteria (16S rRNA gene copy number/g feces) was carried out with quantitative PCR.[19] Sequencing of the pooled libraries was performed on the MiSeq (Illumina) platform using 2x250 bp paired-end reads as described previously.[21]

Bioinformatics

Microbiota composition was analysed using operational taxonomic units (OTUs) obtained from the 16S rRNA sequencing data and clustered at a level of 97% similarity. OTUs were generated from the raw data using a modified version of the VSEARCH pipeline (https://github.com/torognes/vsearch/wiki/VSEARCH-pipeline).[22] The paired fastq files were merged together and quality filtering was performed with a fastq_maxee (maximum expected error value for merged sequences) parameter of 0.5. Sequences longer than 275bp and shorter than 225bp were filtered out. The files were then combined, dereplicated, and all singleton sequences were removed. Sequences were preclustered at 98%, and chimeras were identified and removed from the dataset using the VSEARCH implementation of the UCHIME de-novo algorithm.[23] A secondary chimera detection and removal step was carried out, this time using the UCHIME reference based method and the 'Gold' ChimeraSlayer reference dataset.[24] OTUs were then generated by cluster-

ing the remaining sequences at 97%. OTUs were taxonomically classified to genus level using the assignTaxonomy function in the dada2 R package.[25]

Data analysis and statistics

Descriptive statistics were expressed as median and interquartile range (IQR) or range, or as counts with percentages. In order to show raw data and give the opportunity to compare our data with other studies, we present the results of the first sample as well as all samples together correcting for repeated measurements. For group comparisons, Mann-Whitney U, Chi square and Fishers exact test were used. A p-value of < 0.05 was considered statistically significant. For microbiota data, NMDS analysis was carried out using the phyloseq package in R[26] and permutation ANOVA results were found using the Adonis function in the R vegan package.[27] Significantly different OTUs, genera and families were identified using t-tests on the log-proportional abundances of each OTU/genus. In the cases where the variables of comparison included different time points for the same subjects, paired t-tests were used. Benjamini-Hochberg corrections for multiple testing were applied to the resultant p-values.

Generalized linear mixed models (GLMs) were used to identify relationships between clinical parameters and microbial diversity measures; each model was generated using one variable of interest and the subject's age as explanatory variables with the subject ID included as a random effect. The GLM analysis was carried out using the lme4 package in R.[28] Significance thresholds were applied at 0.05 for unadjusted p-values and 0.1 for adjusted p-values. Adjusted p-values are mentioned in the text. All diversity, evenness and richness measures were found using the appropriate functions in vegan. Correlation tests were performed using the cor.test function in R for unpaired data and using the rmcorr function when analysing repeated measures. Statistics were performed using SPSS version 21 (SPSS, IBM, Armonk) and R version 3.4.3.

RESULTS

Participants' characteristics

Fifteen patients were included between June 2015 and September 2017, with a median age of 4.3 years (range 0.7 – 16.6 years) at study enrolment. The healthy controls were comparable to the patients regarding age, BMI SDS and the proportion of boys/girls. Participants' characteristics are shown in **Table 1.** Eight patients had surgical IF and 7 patients functional IF. Fourteen patients had (re-established) intestinal continuity, while 1 patient had an enterostomy due to chronic intestinal pseudo-obstruction syndrome. A significant higher proportion of patients with functional IF had their ileocecal valve in situ ($p = 0.003$). Four patients underwent surgical lengthening procedures; none in the year prior to sample collection.

All patients were PN dependent at the time of the first sample collection with a median PN duration of 3.6 years (IQR 2.0 - 5.0). Two patients (13%) weaned off PN during the study period after a total PN duration of 1.2 and 2.0 years, respectively; one of them had functional IF and one had surgical IF. Twelve (80%) patients had received antibiotics in the last 2 months before the first sample collection, of them 8/8 with surgical IF and 4/7 with functional IF ($p = 0.04$). Two patients received enteral/oral antibiotic treatment due to suspected bacterial overgrowth and three patients received amoxicillin/clavulanic acid as prokinetic agent. None of the patients received probiotics and none developed D-lactic acidosis during the study period, neither did patients develop intestinal-failure associated liver disease. The median follow-up time i.e. time between the first and last sample of each patient was 14 months (IQR 10 - 21, range 4 - 23).

Table 1. Participant's characteristics at first sample for intestinal failure patients, divided into surgical and functional intestinal failure, and healthy controls

Clinical characteristic	All IF patients n = 15	Surgical IF patients n = 8	Functional IF patients n = 7	Healthy controls n = 25
Sex: boys:girls	8:7 (53:47)	5:3 (63:38)	3:4 (43:57)	13:12 (52:48)
Age at first sample	4.3 (0.7-16.6)	6.1 (0.7-9.9)	3.7 (0.7-16.6)	6.6 (1.1-15.4)
Underlying diseases				
Intestinal atresia	3	3	0	
Gastroschisis (with apple peel atresia and volvulus)	2	2	0	
Necrotizing enterocolitis	2	2	0	
Esophageal atresia with motility problems	1	0	1	
Herniation and strangulation of small bowel	1	1	0	
Chronic intestinal pseudo-obstruction syndrome	1	0	1	
Microvillus inclusion disease	1	0	1	
Protein losing enteropathy based on primary intestinal lymphangiectasia	1	0	1	

Table 1. Participant's characteristics at first sample for intestinal failure patients, divided into surgical and functional intestinal failure, and healthy controls (continued)

Clinical characteristic	All IF patients n = 15	Surgical IF patients n = 8	Functional IF patients n = 7	Healthy controls n = 25
Tricho-hepato-enteric syndrome	1	0	1	
Filamin A mutation with pseudo-obstruction	1	0	1	
Unknown cause	1	0	1	
Whole small bowel in situ	5 (33)	0 (0)	5 (71)	
Remaining small bowel length in cm	65 (30-180)	63 (46-103)	180 (NA)*	
Ileocecal valve in situ	9 (60)	2 (25)	7 (100)	
Enterostomy at first sample	1 (7)	0 (0)	1 (14)	
Partial or total colectomy	5 (33)	4 (50)	1 (14)	
Duration of PN until first sample, years	3.6 (2.0–5.0)	4.4 (1.1-7.3)	3.2 (2.0-4.3)	
PN dependency in %	76 (40-100)	62 (38-87)	82 (67-100)	
Type of nutrition**				
PN only	4 (27)	1 (13)	3 (43)	
PN and tube feeding	7 (47)	4 (50)	3 (43)	
PN and oral nutrition	1 (7)	0 (0)	1 (14)	
PN and tube feeding/oral nutrition	3 (20)	3 (38)	0 (0)	
Mode of tube feeding**				
Continuous	6 (40)	3 (38)	3 (43)	
Bolus	3 (20)	3 (38)	0 (0)	
Combination of continuous and bolus	1 (7)	1 (13)	0 (0)	
Type of tube feeding				
Polymeric	2 (13)	2 (25)	0 (0)	
Semi-elemental	7 (47)	5 (63)	2 (29)	
Elemental	1 (7)	0 (0)	1 (14)	
Antibiotic use 2 months before 1st sample	12 (80)	8 (100)	4 (57)	0 (0)
Antibiotic use at sample because of suspected bacterial overgrowth	2 (13)	5 (63)	2 (29)	NA
Antibiotic use at sample as motility agent	3 (20)	2 (25)	1 (14)	NA
Proton pump inhibitor use	11 (73)	5 (63)	6 (86)	0 (0)
BMI SDS	0.34 (-0.11-1.29)	0.03 (-0.63-0.53)	1.14 (0.40-1.48)	0.07 (-0.67-0.77)

Legend: Values shown as median (IQR) or n (%) unless stated otherwise. * for one patient the small bowel length was not known. ** minimal enteral feeding not included.
Abbreviations: BMI, body mass index; IF, intestinal failure; IQR, interquartile range; PN, parenteral nutrition.

SCFA, BCFA, lactate, sIgA and calprotectin at first sample

A total of 68 fecal samples were collected (median of 3 samples per patient, range 1-10). At the first sample, IF patients had lower concentration of total SCFA (210 μmol/g versus 472 μmol/g per gram dry feces, $p = 0.008$), propionic acid (7.7 μmol/g versus 64 μmol/g, $p < 0.001$) and butyric acid (2.0 μmol/g versus 54.3 μmol/g, $p < 0.001$) than healthy controls (**Table 2, Figure 1**). The median acetic acid level was not different between IF patients and controls, but the proportion of acetic acid was higher in patients than in controls ($p < 0.001$). Patients had a higher concentration of D- and L-lactate than healthy controls (total lactate levels of 3739 μg/g versus 256 μg/g per gram dry feces; $p < 0.001$). Patients with surgical IF had median total lactate levels of 4577 μg/g, 2525 μg/g for L-lactate and 4578 μg/g for D-lactate, whereas these levels were 518 μg/g, 287 μg/g and 298 μg/g for functional IF respectively.

Since patients with IF had significant higher water content, we choose to express data per gram of dry feces. Expressing the same data per mass of wet feces, however, produced similar results (**Supplementary Table 1**). Likewise, when comparing the last sample collected from each participant with the healthy controls and when correcting for sex, age and BMI-SDS, results were generally the same (**Supplementary Table 2**).

Fecal secretory IgA and calprotectin concentrations were only measured in patients and not in the healthy controls. Due to sample availability, calprotectin values were available for 12 patients (80%) at the first sample. Median calprotectin value was 34.95 μg/g (IQR 19.5 - 221, range 19.5 - 814); 7 patients had a calprotectin level < 50 μg/g. The median secretory IgA level at the first sample was 3352 μg/mL and 10 out of 12 patients (83%) had secretory IgA levels above the manufacturer's normal range.

Gut microbiota

We extracted DNA from 66 fecal samples from 14 patients, since for 1 patient the sample amount was inadequate. Four samples could not be amplified, leading to a total of 62 included.

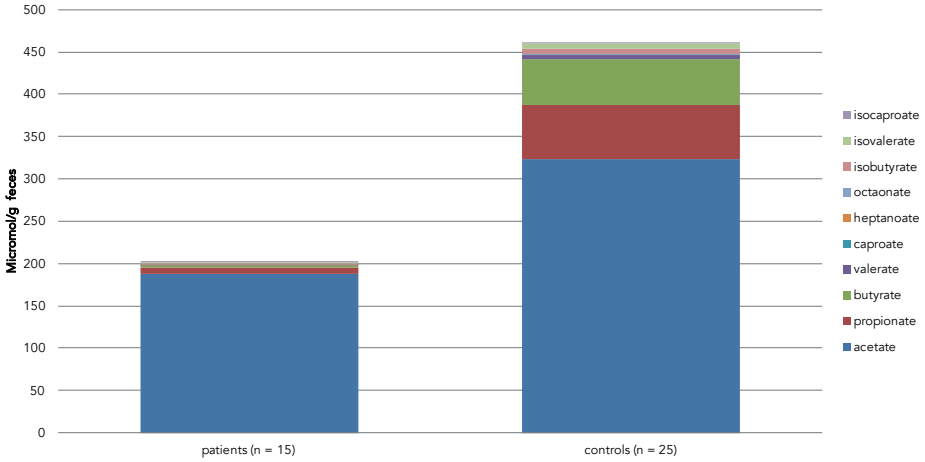
In addition, DNA was extracted from 25 healthy control samples. All these samples were sequenced, of which 7 twice. In total, this yielded 10,382,519 reads, an average of 110,452 reads per sample prior to quality filtering. Twenty percent of the reads were discarded during quality filtering leaving 8,306,581 reads in total. After repeated samples were combined, all samples had greater than 5000 reads and it was agreed that this was sufficient for all samples to be included in the downstream analysis. After OTU clustering, there were 1129 OTUs, 8,306,581 reads, and 87 samples.

Table 2. Fecal water content, concentration of SCFA, BCFA, lactate, secretory IgA, calprotectin and number of 16S rRNA gene copies for IF patients and healthy controls at first sample

	n	Patients with IF n = 15	n	Healthy controls n = 25	p-value
Fecal water content (%)	14	83 (66-87)	25	65 (62-74)	p = 0.011
SCFA (per gram dry feces)	15		25		
Acetic acid (C2), µmol/g		188 (86.8-515)		323 (266-370)	p = 0.074
%		91.8 (83.4-94.4)		67.6 (64.7-61.3)	p < 0.001
Propionic acid (C3), µmol/g		7.73 (1.03-18.6)		64.0 (47.5-85.1)	p < 0.001
%		3.64 (1.19-8.15)		13.7 (10.6-18.8)	p < 0.001
Butyric acid (C4), µmol/g		2.04 (1.08-18.4)		54.3 (36.6-71.0)	p < 0.001
%		0.96 (0.73-4.10)		11.6 (5.60-14.9)	p < 0.001
Valeric acid (C5), µmol/g		0.19 (0.11-5.66)		4.94 (2.04-9.56)	p = 0.001
%		0.18 (0.07-0.65)		1.39 (0.36-2.26)	p = 0.002
Caproic acid (C6), µmol/g		0.45 (0.33-0.62)		0.51 (0.26-3.72)	p = 0.046
%		0.21 (0.07-0.39)		0.12 (0.08-0.78)	p = 0.912
Heptanoic acid (C7), µmol/g		0.71 (0.44-0.87)		0.07 (0.04-0.17)	p = 0.001
%		0.39 (0.11-0.54)		0.01 (0.00-0.05)	p < 0.001
Octanoic acid (C8), µmol/g		0.09 (0.00-0.68)		0.17 (0.04-0.34)	p = 0.659
%		0.05 (0.00-0.37)		0.01 (0.01-0.08)	p = 0.761
Total, µmol/g		210 (103-618)		472 (397-592)	p = 0.008
BCFA (per gram dry feces)	15		25		
Iso-butyric acid (iC4), µmol/g		0.82 (0.18-3.67)		6.40 (3.73-10.2)	p < 0.001
%		0.21 (0.13-1.00)		1.42 (0.92-2.17)	p = 0.003
Iso-valeric acid (iC5), µmol/g		1.05 (0.11-5.66)		6.27 (3.48-10.2)	p < 0.001
%		0.44 (0.13-1.05)		1.18 (0.82-14.9)	p = 0.006
Iso-caproic acid (iC6), mol/g		0.46 (0.18-1.05)		0.35 (0.26-0.48)	p = 0.201
		0.18 (0.09-0.31)		0.07 (0.05-0.09)	p = 0.002
D-lactate, µg/g dry feces	8	1815 (485-7107)	24	79 (58-156)	p < 0.001
L-lactate, µg/g dry feces	8	1923 (464-3675)	24	211 (102-257)	p < 0.001
Total lactate, µg/g dry feces	8	3739 (898-11157)	24	256 (193-376)	p < 0.001
% D-lactate per gram dry feces	8	48 (42-57)	24	33 (19-50)	p = 0.023
Secretory IgA, µg/mL	12	3352 (2340 – 6183)	NA	NM	NA
Calprotectin, µg/g (per gram wet feces)	12	35.0 (19.5-222)	NA	NM	NA
Log of 16S rRNA gene copy per g dry feces (IQR, range)	14	10.7 (9.92-10.9, 0.53-11.5)	25	11.1 (10.9-11.3, 10.7-11.7)	p = 0.003
Log of 16S rRNA gene copy per g wet feces (IQR, range)	14	1.96 (1.60-3.87, 1.28-9.93)	25	3.82 (3.33-4.37, 2.6-18.4)	p = 0.015

Legend: Values shown ad median (IQR) or n (%) unless stated otherwise.
Abbreviations: BCFA, branched-chain fatty acids; IF, intestinal failure; IQR, interquartile range; NA, not applicable; NM, not measured; SCFA, short-chain fatty acids.

Figure 1. Stacked bar chart showing the median levels of short and branched-chain fatty acids (in µmol/g dry feces) for patients and healthy controls



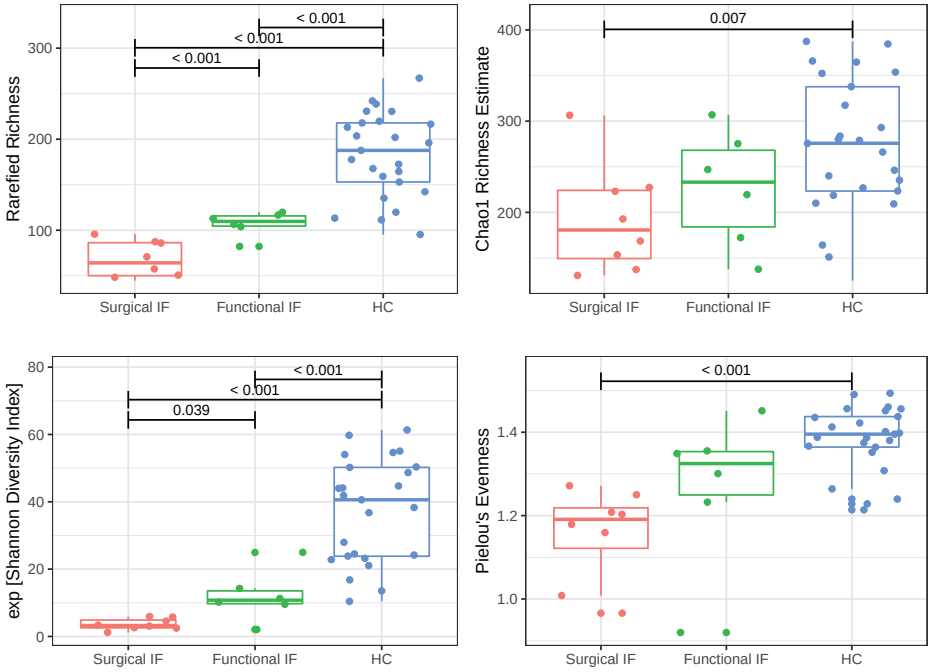
The total bacterial load (16S rRNA gene copies per gram of dry or wet feces) was lower in patients than healthy controls ($p = 0.003$ and $p = 0.015$ respectively). The microbial community structure of IF patients was characterised by a lower Shannon diversity ($p < 0.001$), taxon richness (Chao richness, $p = 0.006$) and evenness (Pielou's evenness, $p < 0.001$) than healthy controls (**Figure 2**). There was no difference in total bacterial load between surgical and functional IF patients. Patients with surgical IF had a lower rarefied richness ($p < 0.001$) and Shannon diversity ($p = 0.039$) than patients with functional IF.

The microbial community structure of IF patients was distinct, clustered separately and presented a higher degree of inter-individual variation from that of healthy controls ($p = 0.002$) (**Figure 3a and b**). Similar analysis was observed using weighted UniFrac distances (**Figure 3c**). Within the IF group, patients with surgical IF tended ($p = 0.009$) to cluster separately from those patients with functional disease whose community structure was less dissimilar and less distant to healthy controls (**Figure 3d**).

Bacteria identified in the fecal samples from patients and healthy controls included those from the 6 dominant phyla of the gut microbiota including Firmicutes, Proteobacteria, Bacteriodetes, Actinobacteria, Verrucomicrobia and Fusobacteria. However, the relative abundance of several phyla was different when compared to controls. IF patients had increased relative abundance of Proteobacteria, whereas they had decreased relative abundance of Bacteroidetes and Verrucomicrobia (**Figure 4**).

At the first sample, the microbiota of IF patients at OTU level was characterised by a higher abundance of taxa belonging to Escherichia-Shigella ($p = 0.006$), Cronobacter ($p = 0.001$) and Staphylococcus (OTU 14, $p < 0.001$) than healthy controls (**Figure 5**).

Figure 2. Alfa diversity in patients with surgical (n = 8) and functional (n = 7) intestinal failure and healthy controls (HC, n = 25)

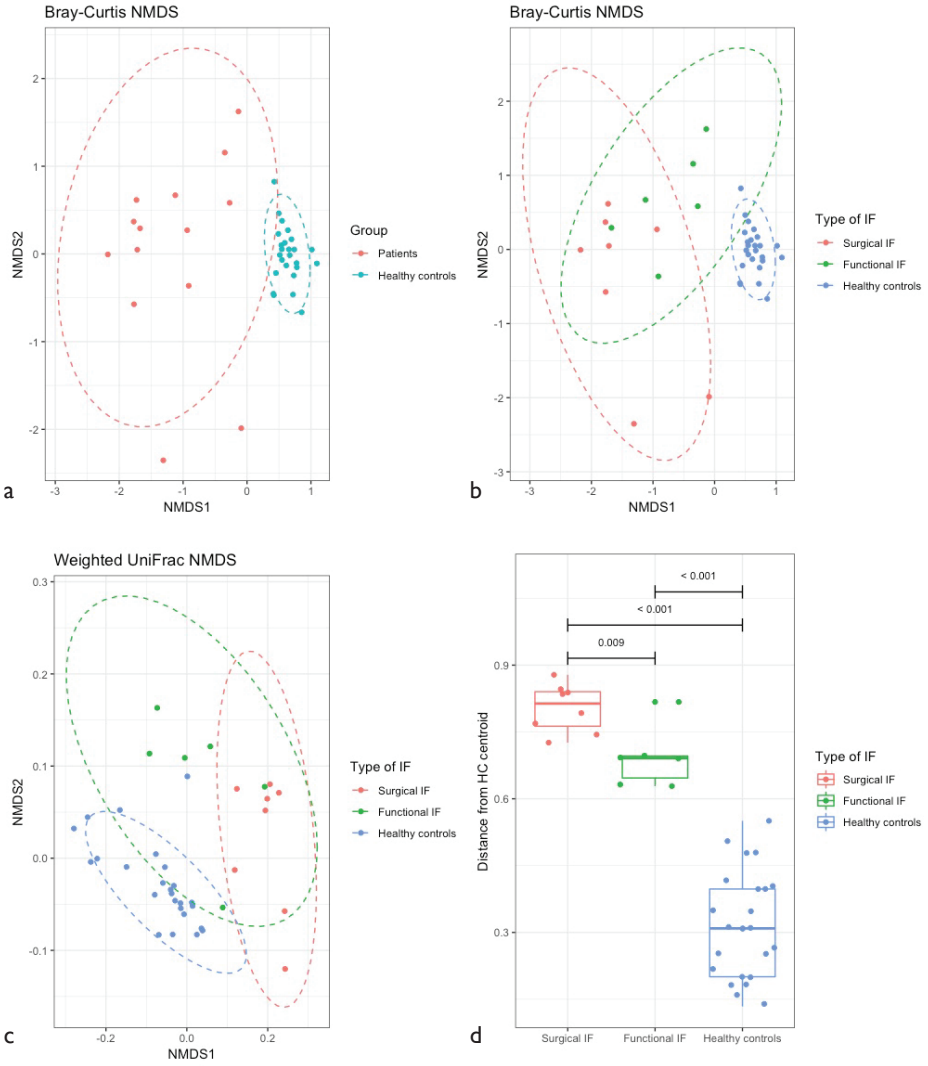


Abbreviations: HC, healthy controls; IF, intestinal failure.

IF patients had a lower abundance of taxa belonging to Faecalibacterium (OTU 114 and 31, p < 0.001) and Ruminococcus 1 and 2 (OTU 83, 167, 262, 42, 119 and 64, p < 0.001). At family level, patients had significant more Enterobacteriaceae (p = 0.001) and Staphylococcaceae (p = 0.001), whereas they had less Bacteroidaceae (p = 0.013) and Bifidobacteriaceae (p = 0.004) (**Supplementary Figure 1**). There were no significant differences in taxon relative abundance at OTU and family level between patients with surgical and functional IF.

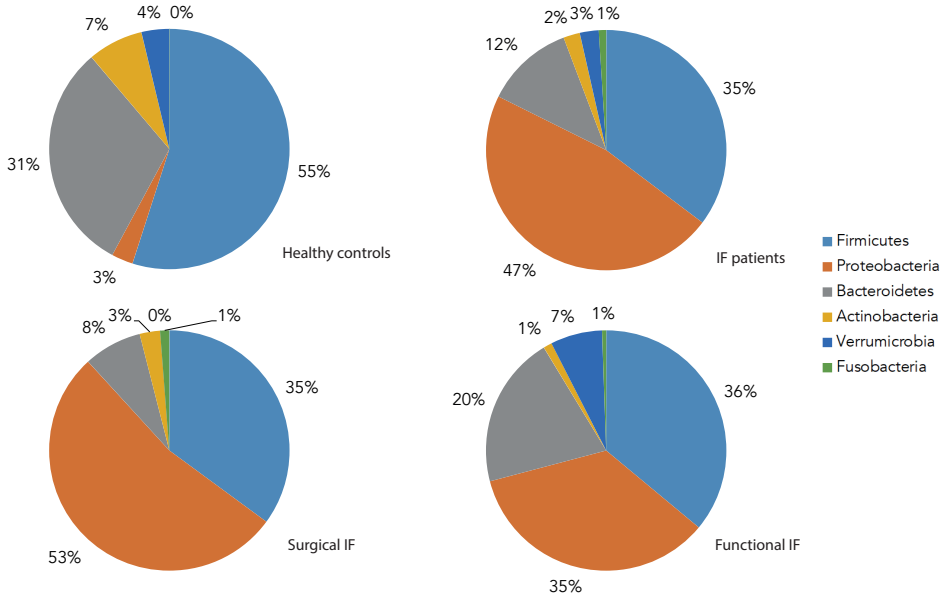
Analysing the data for all samples showed similar results (**Supplementary Table 3 and 4)**. When comparing surgical IF to functional IF patients, surgical IF patients had a higher abundance of taxa belonging to Lactobacillus (OTU 18, 166 and 201, p = 0.003; OTU 38, p = 0.019; OTU 17, p = 0.020; OTU 4, p = 0.037) and Cronobacter (p = 0.020), whereas functional IF patients had a higher abundance of taxa belonging to Lachnoclostridium (OTU 16, p = 0.035l; OTU 45, p = 0.009; OTU 84, p = 0.004 and OTU 22, p = 0.003), Ruminococcaceae (OTU 69, p = 0.012) and Blautia (OTU 93, p = 0.033; OTU 26 and 71, p = 0.031) (**Supplementary Table 5 and 6**).

Figure 3. Non-metric multidimensional scaling (NMDS) of operational taxonomic unit (OTU) community structures for a. intestinal failure patients (n = 15) and healthy controls (n = 25) at the first sample, and b. surgical (n = 8) and functional (n = 7) intestinal failure patients and healthy controls at the first sample. Samples that are clustered closely together are considered to be more similar in terms of microbial species composition than samples that are more separated. c. Weighted UniFrac NMDS of OTU community structures for surgical and functional IF patients and healthy controls at the first sample. d. Bray-Curtis distances from healthy centroid for surgical and functional intestinal failure patients and healthy controls at the first sample.



Abbreviations: IF, intestinal failure; NMDS, non-metric multidimensional scaling; OTU, operational taxonomic unit.

Figure 4. Pie charts representing the major bacterial phyla for surgical, functional and all intestinal failure patients and healthy controls (for all samples)



Abbreviation: IF, intestinal failure.

Gut microbiota and associations with clinical parameters

Using a univariate mixed model to account for the repeated measure design, we analysed associated measures of α-diversity in context with clinical metadata. In all samples analysis, the percentage of PN was negatively associated with Shannon diversity (**Table 3**), and having the whole small bowel in situ was positively associated with Chao richness and rarefied richness. The duration of PN was not significantly associated with % or absolute amounts SCFA and BCFA. The use of antibiotics at or between sample collection was negatively associated with absolute c3, ic4, c4 and c5 levels (**Supplementary Table 7**). The oral/enteral fibre intake was positively associated with absolute levels of c2, c3 and ic5 (**Supplementary Table 8**). Regarding D- and L-lactate, percentage of PN was positively associated with L-lactate (**Supplementary Table 9**). Duration of PN (y) and %PN explained respectively 5.5% and 6.3% of the variation in microbial community structure ($p < 0.01$), and fiber intake (g/kg) 4.8% ($p = 0.01$) (**Table 4**).

Clinical variables associated with OTUs are shown in **Supplementary Table 10**. OTUs belonging to the Genus Bacteroides were positively related to oral nutrition (OTU 13, $p = 0.015$ and OTU 28, $p = 0.032$) and oral/enteral fibre intake (OTU 99, $p < 0.001$, OTU 145 and 32, $p = 0.001$, OTU 13, $p = 0.008$).

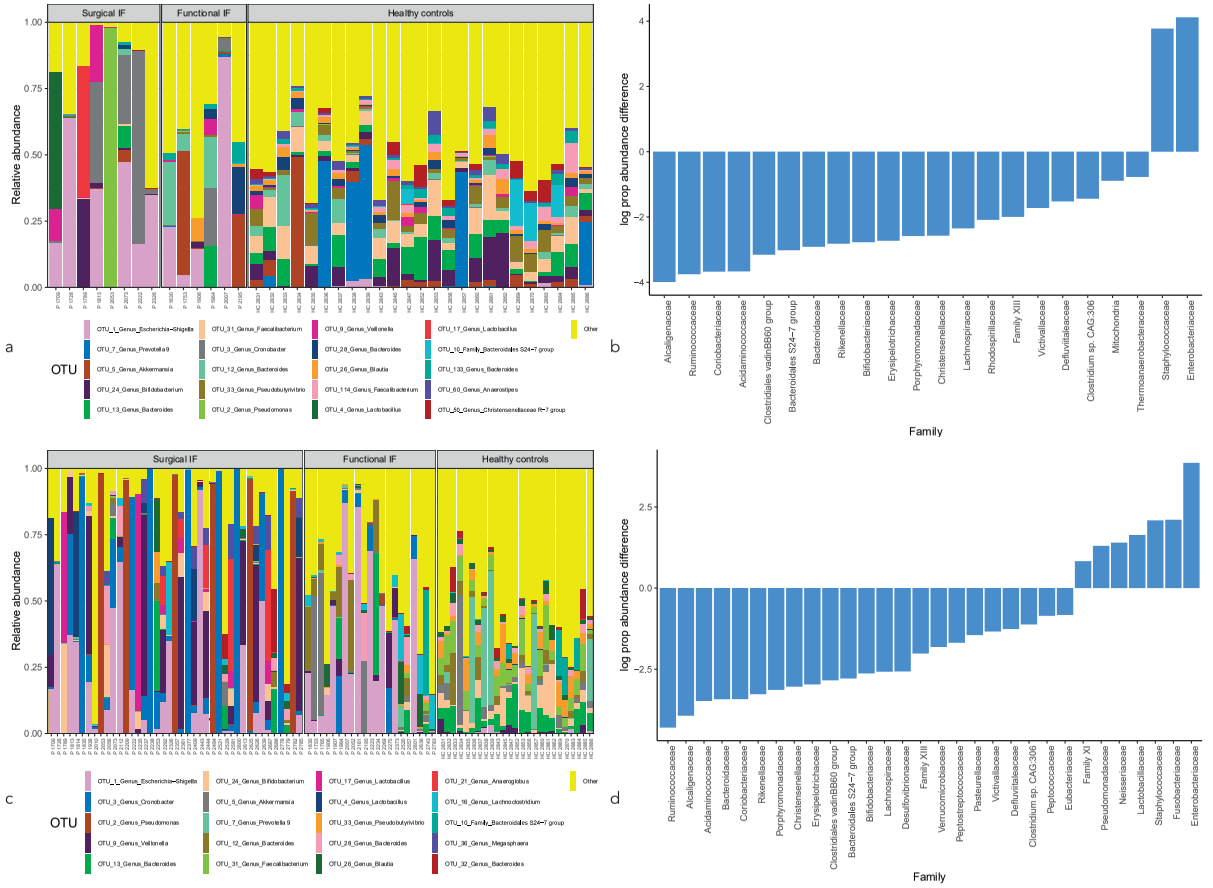


Figure 5.

a. Taxonomic composition of microbiota of paediatric IF patients (n = 15) and healthy controls (n = 25) at operational taxonomic unit (OTU) level for the 20 most abundant OTUs at the first sample

b. Microbial communities in children with IF showing relative abundance of most common taxonomic families at the first sample

c. Taxonomic composition of microbiota of paediatric IF patients and healthy controls at OTU level for the 20 most abundant OTUs for all samples

d. Microbial communities in children with IF showing relative abundance of most common taxonomic families for all samples

Abbreviations: IF, intestinal failure; OTU, operational taxonomic unit.

Table 3. General linear mixed model for clinical variables and Shannon diversity index, Chao richness, Pielou's evenness and rarefied richness

	Shannon diversity		Chao richness		Pielou's evenness		Rarefied richness	
	Beta coefficient	unadjusted p-value adjusted p-value	Beta coefficient	unadjusted p-value adjusted p-value	Beta coefficient	unadjusted p-value adjusted p-value	Beta coefficient	unadjusted p-value adjusted p-value
Nutrition								
Duration of PN (years)	-0.830	0.230 0.688	-4.121	0.306 0.729	0.005	0.729 0.807	-3.991	0.119 0.618
Type of nutrition (PN only, PN+tube feeding, PN+oral nutrition±tubefeeding, tubefeeding/oral nutrition)	0.027 1.855 17.556	0.000 0.001	-45.370 -4.393 40.439	0.021 0.079	0.103 0.059 0.167	0.213 0.300	-28.157 -2.264 44.126	0.001 0.016
Percentage of PN (%)	-0.127	0.001 0.026	-0.333	0.310 0.418	-0.001	0.087 0.180	-0.259	0.164 0.268
Calories of PN divided by REE (%)	-8.132	0.002 0.047	-24.672	0.192 0.298	-0.097	0.073 0.227	-18.620	0.122 0.265
Oral nutrition (yes/no)	6.099	0.021 0.318	37.645	0.046 0.427	.028	0.595 0.768	27.687	0.018 0.318
Oral/enteral fibre intake per kg (g/kg)	20.110	0.017 0.135	-85.295	0.083 0.251	.350	0.024 0.768	-18.263	0.616 0.318
Tube feeding (yes/no)	1.491	0.614 0.732	-39.406	0.045 0.349	.090	0.133 0.474	-18.077	0.153 0.474
Tube feeding type (polymeric, semi-elemental, elemental)	-8.885 8.067	0.009 0.103	10.142 96.316	0.015 0.103	-0.217 -0.005	0.160 0.552	-1.360 61.058	0.017 0.103
Mode of tube feeding (continuous, bolus, both)	-1.965 -3.15	0.806 0.957	-29.706 -35.070	0.290 0.786	-0.031 0.004	0.919 0.957	-23.968 -21.712	0.242 0.786
Gastro-intestinal characteristics								
Whole bowel in situ (yes/no)	7.470	0.052 0.146	69.990	0.000 0.002	0.091	0.282 0.514	43.646	0.000 0.003
Remaining small bowel length (cm)	-0.002	0.970 0.989	-0.011	0.956 0.989	0.001	0.516 0.842	-0.277	0.041 0.605

Ileocecal valve in situ (yes/no)	8.857	0.016 0.098	55.728	0.013 0.098	.048	0.565 0.802	40.515	0.005 0.051
Partial or total colectomy (yes/no)	-4.757	0.194 0.460	-45.038	0.014 0.224	-0.049	0.537 0.716	-31.319	0.008 0.224
Growth								
BMI SDS	-0.489	0.731 0.872	-17.236	0.157 0.852	0.022	0.463 0.852	-5.195	0.507 0.852
Height-for-age SDS < -2 (yes/no)	19.154	0.004 0.044	110.996	0.008 0.059	.134	0.370 0.704	76.935	0.003 0.044
Growing outside target height range (yes/no)	18.328 -4.221	0.013 0.136	112.661 9.482	0.028 0.215	.113 -0.121	0.489 0.722	74.499 -12.973	0.012 0.136
Medication use (yes/no)								
Proton pump inhibitor	-8.814	0.003 0.024	-0.212	0.991 0.991	-0.132	0.029 0.089	-14.412	0.261 0.427
Motility agents	-7.404	0.042 0.087	-14.523	0.501 0.648	-0.233	0.001 0.012	-19.686	0.172 0.267
Cholestyramine	16.201	0.000 0.000	15.310	0.542 0.647	.017	0.772 0.825	39.810	0.064 0.241
Ursochol	-21.685	0.000 0.001	-105.421	0.011 0.080	-0.056	0.543 0.836	-76.505	0.014 0.080
Treatment of bacterial overgrowth	-5.109	0.321 0.623	-28.663	0.321 0.623	-0.038	0.726 0.833	-13.549	0.486 0.696
Antibiotics at sample*	-1.510	0.566 0.784	1.890	0.913 0.967	-0.101	0.046 0.095	2.038	0.860 0.967
Antibiotics between samples	-4.532	0.040 0.089	5.623	0.749 0.844	-0.097	0.031 0.073	-4.612	0.688 0.844
Line sepsis (yes/no)**	-6.984	0.028 0.173	-27.209	0.260 0.537	-0.049	0.435 0.562	-12.810	0.413 0.562

Legend: *Due to bacterial overgrowth, line sepsis or another cause. **with a range of two months before and 2 months after sample collection.
A positive beta coefficient means that the two variables are positively associated, a negative coefficient means that they are negatively associated. For categorical variables the beta coefficients of all categories relative to the first category are mentioned; positive coefficients means that it is more positively associated with higher values of the response variable than the first category.
Abbreviations: BMI, body mass index; PN, parenteral nutrition; REE, resting energy expenditure; SDS, standard deviation score.

Intra-individual variation was very large (**Supplementary Figure 2**). However, when looking at the 2 patients (13%) who weaned off PN during the study period after a total PN duration of 1.2 and 2.0 years, respectively, their microbiota looks more similar to healthy controls (**Figure 6**). When looking at their microbiota, OTUs belonging to Bacteroidetes and Bifidobacteria seem to increase and more different OTUs are present. **Figure 7** shows the composition of the intestinal microbiota according to the proportion of enteral nutrition intake at time of the stool sample collection.

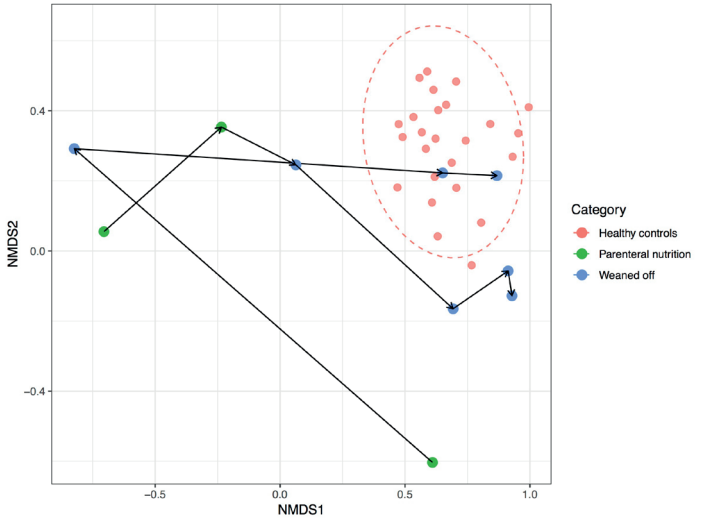
Table 4. Permutation ANOVA analysis for the inter-individual variation in microbiota community structure, attributed to different clinical variables

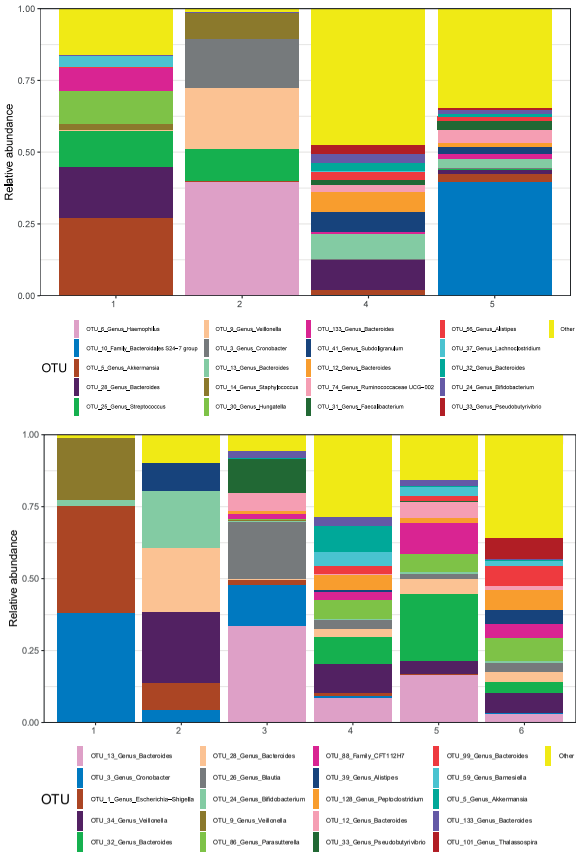
Variable	R^2	p-value
Nutrition		
Duration of PN (years)	0.06	0.005
Type of nutrition (PN, PN±tubefeeding, PN+oral nutrition±tube feeding, tube feeding/oral nutrition)	0.15	0.039
Percentage of PN (%)	0.06	0.005
Calories of PN divided by REE (%)	0.05	0.004
Oral nutrition (yes/no)	0.04	0.522
Oral/enteral fiber intake per kg (g/kg)	0.05	0.011
Tube feeding (yes/no)	0.07	0.221
Tube feeding type (polymeric, semi-elemental, elemental)	0.11	0.339
Mode of tube feeding (continuous, bolus, both)	0.09	0.474
Growth		
BMI (SDS)	0.03	0.965
Height-for-age SDS < -2	0.03	1.000
Growing outside target height range (yes/no)	0.04	1.000
Gastro-intestinal characteristics		
Whole small bowel in situ (yes/no)	0.06	1.000
Remaining small bowel length (cm)	0.06	1.000
Ileocecal valve in situ (yes/no)	0.08	1.000
Partial or total colectomy (yes/no)	0.07	0.308
Medication		
Proton pump inhibitor (yes/no)	0.07	0.209
Motility agents (yes/no)	0.08	0.098
Cholestyramine (yes/no)	0.04	0.869
Ursochol (yes/no)	0.02	0.673
Treatment of bacterial overgrowth (yes/no)	0.05	1.000
Antibiotics at sample (yes/no)*	0.05	0.005
Antibiotics between samples (yes/no)	0.04	0.020
Line sepsis**	0.02	0.134

Legend: *Due to bacterial overgrowth, line sepsis or another cause. **with a range of 2 months before and 2 months after sample collection

Abbreviations: BMI, body mass index; PN, parenteral nutrition; REE, resting energy expenditure; SDS, standard deviation score.

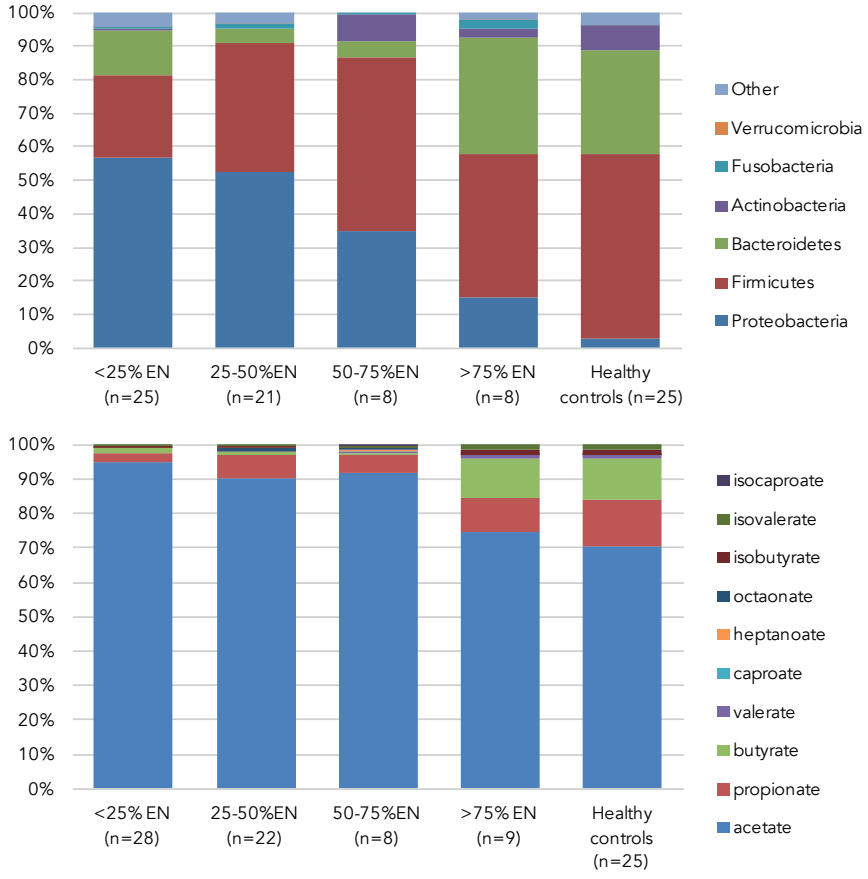
Figure 6.





a. Non-metric multidimensional scaling (NMDS) of operational taxonomic unit (OTU) community structures for the two patients who weaned off parenteral nutrition (PN) during the study period.
b. Taxonomic composition of patients who were able to wean off PN. The patient with functional IF on the upper right was on PN at the first sample, and after that weaned off. The patient on the lower right was on PN at the first two samples and after that weaned off and had surgical IF.

Figure 7. a) Composition of the intestinal microbiota and b) amount of short-chain fatty acids and branched-chain fatty acids according to the proportion of enteral nutrition intake at time of the stool sample collection



During the study period, three patients were suspected of small intestinal bacterial overgrowth and were treated with antibiotics. The microbial community structure was not different between the samples of patients suspected of bacterial overgrowth versus those not suspected of bacterial overgrowth.

DISCUSSION

The aim of this study was to prospectively characterise the fecal microbiota composition and its metabolic activity of paediatric IF patients and relate it with clinical characteristics in a longitudinal way. Similar to previous reports, the gut microbiota of children with IF presents distinct characteristics of microbial dysbiosis, both in terms of composition as well as diet-related functionality.[5-7,29,30] The bacterial diversity and richness, presumptive markers of optimal gut health, were markedly reduced in IF patients compared to healthy controls, and the microbial structure of the former was distinct to that of the latter group. When we looked at the taxon relative abundance of these two groups, patients with IF had a higher relative abundance of Proteobacteria, an observation which is consistent with previous studies.[5-7,9] A parallel decrease in the abundance of Firmicutes and Bacteroidetes was found, as described previously.[9,30,31]

Proteobacteria and other species whose relative abundance was increased in IF patients normally represent a very small fraction of the gut microbiota. Many species belonging to the Proteobacteria phylum are opportunistic pathogens, such as *E. coli*, *Klebsiella* and *Cronobacter*. The clinical significance of this observation is yet unclear. Their increased relative abundance and their metabolites in conjunction with a compromised gut barrier function and suppression of beneficial species may increase translocation of bacterial metabolites such as Lipopolysaccharides. This may induce an immune response, potentially affecting clinical outcomes and disease prognosis in this population.[32] More specifically, *Cronobacter,* which can invade intestinal cells and the blood-brain barrier, has been related to various infections including bacteremia and necrotizing enterocolitis.[33]

The features of microbial dysbiosis observed in this study are not unexpected and is in agreement with our hypothesis. Changes in normal gastro-intestinal anatomy and physiology are among the main contributing factors of the microbial dysbiosis. Extensive small bowel resection alters intestinal environment, including lowering of luminal pH, increasing oxygen concentration and disrupting the enterohepatic circulation of bile acids.[34-36] Other factors that might play a role are the rapid transit time and the large amount of undigested nutrients that are presented at the remaining colon for bacterial usage.[37] This may all lead to proliferation of aerobic bacteria at the expense of anaerobic bacteria. Indeed in this study we have observed differences in the microbial community structure between patients with surgical IF and those with IF owing to loss of gut function but having their gut in situ. Functional IF patients had a microbial community structure more similar to healthy controls than surgical IF patients. Moreover, patients with functional IF had a lower abundance of taxa belonging to Lactobacillus and Cronobacter. One previous study including both patients with surgical and functional IF[6] did not evaluate differences between these groups.

The lack of fermentable substrate necessary for anaerobic bacteria growth, such as fibre- and resistance starch, might explain the staggering decrease in fibre fermenting species belonging to Firmicutes and Bacteroidetes. This decrease of in main producers of SCFA has a significant impact, as shown by lower total as well as most individual SCFA levels. This is in contrast with one previous study including infants with short bowel syndrome, showing only differences in fecal acetate concentration.[7] SCFA stimulate vascular flow, motility, increase sodium absorption, affect cell proliferation and differentiation and enhance the immune system.[11-13] They inhibit the growth of potentially harmful bacteria and promote the growth of beneficial bacteria. In addition, acetate contributes to the energy requirements of the host by absorption by the colon.[38]

Next to a decrease of Firmicutes and Bacteroidetes, Proteobacteria can metabolise broader substrates and therefore are more resilient to changes in the diet of the host.[39] We showed that the higher amount of enteral nutrition patients received, the less Proteobacteria they had, in accordance with previous studies.[5,6,29,40] Also, when we looked at the microbiota of patients whose gut adapted, diversity increased and their overall microbial structure moved closer to that of the healthy controls. Moreover, selective species such as Bacteroides and Bifidobacterium appeared to bloom in patients whose gut adapts over time.

The dominance of lactate producing bacteria and the decreased abundance of lactate consuming bacteria[39 41,42], results in the production of both D- and L-lactate, as we observed in this study. We did observe higher values of lactate in surgical IF patients, in agreement with the fact that they had a higher relative abundance of Lactobacillus than functional IF patients. In contrast to previous studies[6,7], we were not able to relate this to D-lactic acidosis as none of the patients in our study developed this condition.

Murine studies have shown that PN results in decreased levels of secretory IgA. In contrast, most of our patients had high values of secretory IgA. In addition, most patients had normal calprotectin levels. A previous study showed that fecal secretory IgA and calprotectin did not differ between infants with short bowel syndrome and healthy controls.[7] Because of limited amount of feces available, we were not able to measure secretory IgA and calprotectin levels in healthy controls. The fact that most patients had normal calprotectin levels might be explained by the fact that there is no involvement of neutrophils or macrophages in small intestinal bacterial overgrowth, although previous studies reported conflicting results.[43,44]

The strengths of our study are the longitudinal nature of the study and the analysis we performed with prospectively collected clinical metadata. Another strength is the fact that all patients with IF including those with functional IF were included. However, one of the limitations was the relatively small sample size. Since IF is a rare condition, it is

difficult to perform single center studies with large sample sizes. Future research should therefore be preferably multi-center. Microbiota analysis was only performed on fecal samples and therefore may not reflect the mucosal microbiota. Obtaining biopsies for microbiota analyses, however, was not possible since we do not routinely perform endoscopies. Moreover, including endoscopies in our study protocol may be unacceptable for institutional review board approval. Another limitation was the fact that the majority of patients received antibiotics within 2 months prior to sample collection. Several previous studies have shown how antibiotics influence the microbiota.[45-47] However, this reflects clinical practice and the population typically treated by IF teams.

Changes in the gut microbiota may be used as biomarker to judge the optimal time of transition from PN to enteral nutrition. Since SCFA are altered in patients with IF, future studies following patients during the process of intestinal adaptation from the start of IF onwards should also include SCFA measurements as well as the species that are increased after weaning off PN.

Furthermore, the altered microbiota may be a therapeutic target. Currently, many IF patients receive broad-spectrum antibiotics because of suspected small intestinal bacterial overgrowth. However, this may further reduce the abundance and diversity of the normal beneficial microbiota and targeted antibiotics may be more beneficial. Prebiotics, probiotics or synbiotics may also be valuable, particularly during the active process of gut adaptation and transition from PN to enteral nutrition feeding.[48] However, cases of bacteremia due to probiotics have been reported too.[49] It is not well known how pro-/prebiotics act in a non-physiological environment after surgical resection. There are no clear guidelines if fiber should be supplemented and how much fiber should be used, but the findings of this study are supporting this practice.[50] Future studies should therefore evaluate the response to fiber therapy and also focus on type and dose of these fibers, especially since the composition of the microbiota also influences the fermentation of fiber.[42] Another therapeutic option might be fecal microbial transplantation, which has recently been performed in a pediatric IF patient with therapy a resistant D-lactic acidosis.[51] However, risks of fecal transplantation such as bacterial translocation and sepsis are currently not well understood, as well as the duration of the effect of transplantation in this specific population.

In summary, we have observed pronounced differences in the composition and metabolic activity of the fecal microbiota; not only between paediatric IF patients and healthy controls, but also within different subtypes of IF. The extent of dysbiosis appears to resolve as the patients adapt their gut and transit from PN to oral and tube feeding. Future research should explore whether these differences precede or follow gut adaptation; hence the role they may play in adjusting clinical practice based on the gut microbiome during this process. Association between dysbiosis features and

clinical outcomes, including small intestinal bacterial overgrowth and D-lactic acidosis and PN associated liver disease should be explored in future prospective research. In case of positive results, active manipulation of the gut microbiota during gut adaptation can improve patients' outcomes. These findings may offer new opportunities to use the microbiota and its metabolic aspects as a diagnostic marker and/or therapeutic target.

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Health-related quality of life, anxiety, depression and distress of mothers and fathers of children on home parenteral nutrition

Clin Nutr. 2018 Jul 2. pii: S0261-5614(18)31200-7. doi: 10.1016/j.clnu.2018.06.981.

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ABSTRACT

Background & aims

Parents of children with intestinal failure, dependent on Home Parenteral Nutrition (HPN), may experience psychosocial problems due to the illness and intensive treatment of their child. Literature concerning psychosocial problems is scarce. Therefore, we aimed to investigate Health-Related Quality of Life (HRQOL), levels of anxiety, depression, distress and everyday problems of these mothers and fathers.

Methods

A multicenter study was conducted among 37 mothers and 25 fathers of 37 children on HPN (response-rate 37/49 = 76%, mean age children = 5.1 years, SD = 4.6). Parents completed three questionnaires to measure different outcomes on the KLIK website (www.hetklikt.nu): the TNO-AZL QOL Questionnaire (TAAQOL) to measure HRQOL, the Hospital Anxiety and Depression Scale (HADS) to measure anxiety and depression, and the Distress Thermometer for Parents (DT-P) to measure distress. Scores were compared to Dutch reference mothers and fathers using Mann-Whitney U-tests.

Results

No differences were found in HRQOL, measured by the TAAQOL, between HPN parents compared to the reference groups, except for the subscale 'depressive emotions' for mothers (p=.01) and 'daily activities' for fathers (p=.04). HPN mothers reported higher levels of depression compared to reference mothers (p=.001). In addition, HPN mothers and fathers reported higher levels of distress than reference mothers (p=.001) and fathers (p=.03). HPN mothers reported significantly more problems in the practical, emotional, cognitive and parenting domains, fathers in the social, emotional and parenting domains.

Conclusions

On HRQOL, anxiety and depression, HPN parents generally did not show much differences compared to reference parents. However, when asked about parental distress and everyday problems, HPN treatment of their child seems highly stressful for some parents and influences daily functioning. Therefore, structural screening for parental psychosocial problems in clinical practice, e.g. using the DT-P, is necessary in order to improve the well-being of both these parents and their children dependent on HPN.

INTRODUCTION

Intestinal failure, characterized by inadequate absorption of food or fluids for adequate growth, is a condition requiring the use of parenteral nutrition (PN) as long as the intestinal failure persists.[1] PN is an artificial nutritional technology whereby nutrients are administered intravenously in the hospital, and can be safely administered at home by well-trained caretakers (HPN).[2] Because prolonged hospitalizations impair children's and families' quality of life, an HPN program should be considered when a child needs PN for more than three months.[3] Reported prevalence of HPN varies across studies ranging from 9.6 children per million in the Netherlands to 13.7 children per million in the UK.[4,5] The parents must be educated in catheter care and the procedures necessary to connect and disconnect the PN to the central line. In addition, parents often are responsible for other nursing procedures, such as providing tube feeding and taking care of a stoma. This treatment is complex, of high risk for complications and will put much social and psychological pressure upon the child and parents.[6]

Parents spend on average over 2 h a day on preparing and connecting the infusions. The burden on parents is high, as the majority cannot rely on someone else to connect or disconnect the parenteral nutrition.[7] In addition, hospitalizations are common due to their child's underlying disease but also complications such as the loss of vascular access or sepsis.[8] A French study showed that these hospitalizations occur on average at least twice a year.[9]

In the last decade, survival rates for patients with intestinal failure have significantly improved, causing Health-Related Quality of Life (HRQOL) to be a new focus of interest.[10] Despite the large impact HPN has on the daily life of children and their families, little is known about parental HRQOL and the psychosocial consequences for these parents, and results are quite ambiguous (**Table 1**). Only two quantitative studies on this topic using validated questionnaires were carried out. Gottrand et al.[11] found that parental QOL, measured with the French Subjective QOL Profile questionnaire, was significantly impaired, especially for mothers. Wong et al. showed that seven of the 11 parents of children on HPN exceeded the threshold for psychiatric morbidity, and described a significant deterioration before and after the child's disease for social life, family life, sex life and work compared with controls.[12] In two qualitative studies, families with children on HPN seemed to cope well[13] and were resilient.[14] However in two other qualitative studies, mothers of children on HPN reported fear, frustration, anger and isolation[15] and nursing their child at home was a huge physical and psychological burden to parents.[16]

In conclusion, only six studies were conducted.[11-16] Therefore, more quantitative, recent studies on functioning of parents, including both fathers and mothers of a child dependent on HPN are needed. It is essential to gain more insight into how these parents are functioning psychosocially in order to decide if, and which kind of help is required.

Therefore, the aims of this study are to determine the 1) HRQOL, 2) degree of anxiety and depression, and 3) levels of parental distress and everyday problems in mothers and fathers of a child dependent on HPN (HPN mothers and fathers) compared to Dutch reference mothers and fathers.

Table 1. Summary of previous studies on parents of children on HPN

First author	Year	Short title	Country	N of participants	Questionnaire	Type of study	Main findings
Gottrand	2005	Life satisfaction in children on HPN and their families	France	68 mothers and 62 fathers	Subjective QOL Profile questionnaire	Quantitative	Parental QOL was impaired, especially for mothers. Mothers lower level of satisfaction than fathers on work, inner life, and freedom.
Wong	2000	QOL of parents of children on HPN	UK	11 parents, gender unknown	General Health Questionnaire (GHQ-28)	Quantitative	7/11 parents exceeded the threshold for psychiatric morbidity. Significant deterioration before and after child's disease for social life, family life, sex life and work compared with controls. Parents more physically tired, difficulties in taking holidays, going shopping and spending time with their partners. Many felt frustrated, annoyed, stressed and having problems sleeping.
Carlsson	1997	HPN in children in Sweden	Sweden	12 parents, gender unknown	n/a	Qualitative	Families seemed to cope well. Parents were successful and skilled caregivers, and many carried on with their professional careers. However, the interviews did not cover family stress or interpersonal relation problems.
Kawakami	2013	Experiences of parents with children on HPN	Japan	5 mothers and 1 father	n/a	Qualitative	Families were resilient. Information about child's health status and care plan were important. Relationship with healthcare providers minimizes stress responses.
Silver	2004	The lived experience of HPN	USA	3 mothers	n/a	Qualitative	Mothers reported fear, frustration, anger and isolation, and intense awareness of potential adverse events related to HPN use.
Sexton	2005	Homecare packages for paediatric HPN patients	UK	20, over half were mothers	n/a	Qualitative	All the families expressed immense physical, psychological issues and burden of care.

Abbreviations: HPN, home parenteral nutrition; QOL, quality of life.

MATERIALS AND METHODS

Participants and procedures

This study was conducted during 2012-2016 in mothers and fathers of children dependent on HPN, and undergoing treatment in the Emma Children's Hospital/Academic Medical Center Amsterdam or Sophia Children's Hospital/Erasmus Medical Center Rotterdam, the Netherlands. Inclusion criteria were, parents: 1) of children aged 0-18 years, 2) of children receiving HPN for ≥3 months, 3) should be able to complete Dutch questionnaires. For this study, we used data from the KLIK database. Parents were invited by a letter of the HPN team to register themselves on the KLIK website (www.hetklikt.nu) as part of standard care. KLIK is an online portal, to systematically monitor different aspects of children with various chronic diseases and their parents over time. Parents and children are asked to complete Patient Reported Outcome Measurements (PROMs) about HRQOL and psychosocial functioning one week prior to the outpatient consultation with the pediatrician or other healthcare professional.[17] Answers on the PROMs are converted into a KLIK PROfile and discussed during the consultation. In this way, communication on psychosocial topics between the patient/parent and the pediatrician is increased, and problems can be detected at an early stage.[18,19] For this study, we used the questionnaires completed for the first time on the KLIK website by the HPN parents, and only of parents who gave online informed consent for use of their data for scientific purposes. The Medical Ethics Committee of both hospitals approved the study.

Measurements

Sociodemographics and medical characteristics

Mothers or fathers completed an online questionnaire concerning their socio-demographic characteristics: age, country of birth, educational level, employment status, marital status, number of children living at home, and age, gender and education of their child on HPN. Information regarding underlying disease of the child, duration of PN and HPN, and number of hospital admissions in the past six months and since the start of HPN was provided by the healthcare professionals.

Health-Related Quality of Life

Parental HRQOL was assessed with the TNO-AZL Questionnaire for Adult's HRQOL (TAAQOL).[20] This validated questionnaire measures health status problems weighted by the impact of problems on well-being on 12 scales (see **Table 3**). Higher scores indicate a better HRQOL (range 0-100). The psychometric properties, validity and reliability of the TAAQOL were satisfactory.[20] Cronbach's alpha values, indicating internal consistency, in the present study were moderate to good, ranging from .53-.91 for mothers and .70-1.00 for fathers. We used reference data of Dutch mothers and fathers of healthy children.[21]

Anxiety and Depression

Parental anxiety and depression were assessed with the Hospital Anxiety and Depression Scale (HADS).[22] This questionnaire is divided into two 7-item scales, with answers on a four-point scale (0–3). Higher scores indicate a higher level of anxiety or depression (range 0-21). A scale score of ≥8 (cut-off score) indicates clinically significant anxiety or depression. The Dutch version of the HADS showed satisfactory validity and reliability.[23] In the present study, Cronbach's alpha values were moderate to good; .74-.78 for mothers and .64-.84 for fathers. A reference group of Dutch mothers and fathers is available.[24]

Parental distress

Parental distress and everyday problems were assessed with the Distress Thermometer for Parents (DT-P)[25], a validated screening instrument frequently used in clinical practice to quickly identify distress and everyday problems in parents of children with a chronic condition. The DT-P consists of 1) a 'thermometer' ranging from 0 (no distress) to 10 (extreme distress) on which parents rate their overall distress in the past week, where a score ≥4 indicates clinically elevated distress, 2) a problem list which inquires the occurrence ('yes' or 'no') of 36 or 34 everyday problems, (depending on the age of the child; <2 years or ≥2 years, respectively) across six problem domains where problem domain scores are the sum of item scores (yes=1, no=0) within that problem domain, and 3) additional questions (see **Table 5a**) and an open question. In developing the DT-P, we distinguished the parenting problem domain into two age categories (<2 years or ≥2 years) because, based on reactions of social workers and psychologists, the problems in parenting are different for these age categories.[25] Cronbach's alpha values in the present study were moderate to good, ranging from .54-.88 for mothers and .59-.91 for fathers. A reference group of Dutch mothers and fathers of healthy children is available.[26]

Statistical analyses

The Statistical Package for Social Sciences (SPSS) version 24 was used for all statistical analyses. First, socio-demographic characteristics of mothers, fathers and children were analyzed using descriptive analyses. Participants and non-participants were compared on age, gender of the child and underlying diagnosis, using an independent samples t-test and Chi-square tests, respectively. Second, HRQOL differences between HPN mothers and fathers and mothers and fathers in the reference groups were non-parametrically analyzed using Mann-Whitney U-tests. By calculating the effect size (r), the extent of the differences between both groups was measured. An effect size of .10 was considered as small, .30 was considered as medium and .50 was considered as large.[27] Third, the proportion of HPN mothers and fathers scoring in the clinical range (score ≥8) on anxiety or depression was compared to the proportion of mothers and fathers in the reference groups scoring in the clinical range, using Chi-square tests. In addition, median levels

of anxiety and depression were compared using Mann-Whitney U-tests. Odds ratios (OR) and effect sizes (r) were calculated. Fourth, median DT-P thermometer and domain scores of HPN mothers and fathers were compared with scores of reference mothers and fathers using Mann-Whitney U-tests. Chi-square tests were used to test differences in clinical thermometer score (≥4), everyday problem scores and additional questions. Odds ratios (OR) and effect sizes (r) were calculated. Answers on the open question of the DT-P were described explorative.

RESULTS

Socio-demographics and medical characteristics

In total, parents of 49 children dependent on HPN were eligible and 62 parents (37 mothers, 25 fathers) of 37/49 (76%) children completed one or more questionnaires (response rate AMC: 81%, Erasmus MC: 65%). Mean age of the child did not differ (p = .81) between participants (N = 37, M = 5.1 years, SD = 4.6) and non-participants (N = 12, M = 4.7 years, SD = 6.2), neither did gender (46% vs 33% female, p = .44) or underlying diagnosis. Characteristics of the participating parents and their children are shown in **Table 2**. Mean duration of HPN was 3.1 years (SD 2.9). Most children suffered from chronic intestinal pseudo-obstruction syndrome (32%), short bowel syndrome (22%) or intestinal obstruction due to congenital malformations (19%).

Table 2. Socio-demographic characteristics of mothers and fathers of a child on Home Parenteral Nutrition

	Mothers (N=37)	**Fathers (N=25)**
Age in years, M (SD), median, range	36.0 (8.2), 36.4, 23.4-55.1	40.0 (8.6), 38.9, 29.2-60.4
Born in the Netherlands, N (%)	31 (83.8%)	21 (84.0%)
Educational level, N (%) [a, b]		
Low	7 (18.9%)	0 (0.0%)
Intermediate	19 (51.4%)	14 (58.3%)
High	11 (29.7%)	10 (41.7%)
Paid employment, N (%)	17 (45.9%)	23 (92.0%)
Marital status, N (%) [b]		
Married/living together	35 (94.6%)	24 (100.0%)
Single/separated	2 (5.4%)	0 (0.0%)
Children living at home, N (%)		
1	12 (32.4%)	7 (28.0%)
2	14 (37.8%)	11 (44.0%)
≥ 3	11 (29.8%)	7 (28.0%)
	Children on HPN (N=37)	
Age in years, M (SD), median, range	5.1 (4.6), 3.6, 0.3-17.4	
Female gender, N (%)	17 (45.9%)	
Undergoing treatment in, N (%)		
Amsterdam (AMC)	26 (70.3%)	
Rotterdam (Erasmus MC)	11 (29.7%)	
Duration of PN in years, M (SD), median, range	3.5 (3.0), 3.1, 0.2-10.2	
Duration of HPN in years, M (SD), median, range	3.1 (2.9), 2.6, 0.1-10.0	
Underlying disease, N (%)		
Chronic intestinal pseudo-obstruction syndrome	12 (32%)	
Short bowel syndrome	8 (22%)	
Intestinal obstruction due to congenital malformations	7 (19%)	

Table 2. Socio-demographic characteristics of mothers and fathers of a child on Home Parenteral Nutrition (continued)

	Mothers (N=37)	Fathers (N=25)
Microvillous inclusion disease	4 (11%)	
Chronic intractable diarrhea	4 (11%)	
Hirschsprung's disease	1 (3%)	
Severe failure to thrive	1 (3%)	
Number of admissions in past 6 months, M (SD), median, range [c]	1.1 (0.9), 1, 0-3	
Number of admissions since start HPN, M (SD), median, range [d]	8.3 (10.2), 2, 0-36	
Education, N (%)		
None (yet)	15 (40.5%)	
Daycare	6 (16.2%)	
Regular primary school	8 (21.6%)	
Special primary school	5 (13.5%)	
Regular secondary school	2 (5.4%)	
Special secondary school	1 (2.7%)	

Legend: [a] Highest educational level completed. Low: primary education, lower vocational education, lower or middle general secondary education; Intermediate: middle vocational education, higher secondary education, pre-university education; High: higher vocational education, university. [b] Score of 1 father missing. [c] Scores of 4 children missing. [d] Scores of 3 children missing.
Abbreviations: HPN, home parenteral nutrition; PN, parenteral nutrition.

Health-Related Quality of Life

HRQOL of HPN parents did not differ significantly from HRQOL of parents of healthy children on 11 of 12 TAAQOL scales (**Table 3**). Only on the 'depressive emotions' scale, mothers showed a significantly lower median score compared to reference mothers (75 vs 83, p = .01, r = -.13). On the 'daily activities' scale, fathers showed a significantly lower score compared to reference fathers (88 vs 100, p = .04, r = -.21).

Anxiety and depression

The proportion of HPN mothers and fathers scoring in the clinical range (score ≥8) on anxiety or depression did not differ significantly from mothers and fathers in the reference groups (**Table 4a**). However, when medians were compared, HPN mothers showed significantly higher levels of depression than reference mothers (p = .001, r = -.16). (**Table 4b**).

Parental distress

Thermometer score

When comparing DT-P thermometer median scores, both HPN mothers (5 vs 3, p = .001) and fathers (3 vs 2, p = .03) reported significantly higher overall distress than reference mothers and fathers. Only HPN mothers reported significantly more often elevated distress (score ≥4) than mothers of healthy children (64.9% vs 42.3%, p = .007), see **Table 5a**.

Table 3. HRQOL (according to the TAAQOL) of mothers and fathers of children on HPN compared with reference groups of mothers and fathers of healthy children

	HPN mothers			Reference mothers					HPN fathers			Reference fathers				
HRQOL	**N**	**Med**	**IQR**	**N**	**Med**	**IQR**	***P***	**r**	**N**	**Med**	**IQR**	**N**	**Med**	**IQR**	***p***	**r**
Gross motoric functioning	35	100	88-100	359	100	81-100	.18	-.07	24	100	100-100	73	100	100-100	.96	-.01
Fine motoric functioning	35	100	100-100	358	100	100-100	.08	-.09	24	100	100-100	73	100	100-100	.96	.00
Cognitive functioning	35	88	63-100	358	88	63-100	.49	-.03	24	94	66-100	72	97	75-100	.52	-.07
Sleep	35	63	44-94	360	75	50-94	.25	-.06	24	84	56-100	72	81	56-100	.86	-.02
Pain	35	81	63-94	361	75	56-88	.12	-.08	24	88	64-100	72	81	64-100	.67	-.04
Social functioning	35	88	69-100	356	88	75-100	.47	-.04	24	84	52-100	73	94	75-100	.13	-.16
Daily activities	35	100	63-100	355	94	75-100	.79	-.01	24	88	58-100	73	100	88-100	**.04**	-.21
Sexuality	35	100	88-100	341	100	75-100	.20	-.07	24	100	50-100	73	100	69-100	.67	-.04
Vitality	35	58	33-75	360	67	46-75	.09	-.08	24	67	42-75	73	75	58-83	.08	-.18
Positive emotions	35	67	42-75	359	67	58-75	.53	-.03	24	67	60-73	73	67	58-75	.82	-.02
Depressive emotions	35	75	67-83	360	83	67-92	**.010**	-.13	24	83	75-92	73	83	75-92	.21	-.13
Aggressive emotions	35	89	78-100	358	89	78-100	.39	-.04	24	89	89-100	73	100	89-100	.40	-.08

Legend: Higher scores indicate a higher HRQOL. P-values according to Mann Whitney U-tests. Significant differences at $p < .05$ are presented in bold.
Abbreviations: HPN, home parenteral nutrition; HRQOL, Health-Related Quality of Life; TAAQOL, TNO-AZL Questionnaire for Adult's HRQOL; Med, Median; IQR, interquartile range.

Problem domain scores

HPN mothers reported a significantly higher total problem score than mothers of healthy children (6 vs 4, p = .006). HPN fathers did not differ significantly on total problem score (6 vs 2, p = .13). Both HPN mothers and fathers reported more problems on 4 out of 7 problem domains, compared to mothers and fathers of healthy children; mothers reported more problems in the practical, emotional, cognitive and parenting (≥2 years) domain, fathers reported more problems in the social, emotional, parenting (≥2 years) and parenting (<2 years) domain. Effect sizes (*r*) ranged from -.08 to -.24.

Everyday problem scores

In total, mothers reported significantly more problems on 15/34 everyday problems when their child was ≥2 years, or 12/36 everyday problems when their child was <2 years (**Table 5b**). HPN mothers reported significantly less problems about work/study than

Table 4a. Clinical scores of anxiety and depression: score of ≥8 in HPN mothers and fathers compared with reference groups of mothers and fathers: percentages and Odds Ratio (OR)

	Mothers							Fathers						
	HPN (N=34)		Reference (N=368)					HPN (N=24)		Reference (N=368)				
	N	%	N	%	*p*	OR	95% CI of OR	N	%	N	%	*p*	OR	95% CI of OR
Anxiety	9	26.5	76	20.7	.43	1.39	.62-3.13	2	8.3	64	17.4	.40*	.43	.10-1.89
Depression	5	14.7	44	12.0	.64	1.27	.47-3.45	4	16.7	56	15.2	.77*	1.11	.37-3.33

Legend: Differences according to Chi-square tests. *=Fishers Exact (N<5 in one cell)
Abbreviations: CI, confidence interval; HPN, home parenteral nutrition; OR, odds ratio.

Table 4b. Median scores of anxiety and depression in HPN mothers and fathers compared with reference groups of mothers and fathers

	Mothers						Fathers					
	HPN (N=34)		Reference (N=368)				HPN (N=24)		Reference (N=368)			
	Median	IQR	Median	IQR	*p*	Effect size r	Median	IQR	Median	IQR	*p*	Effect size r
Anxiety	4	3-8	4	2-7	.39	-.04	4	2-5.75	3	1-6	.64	-.02
Depression	4	2-6.25	2	1-5	**.001**	-.16	4	1-6	2	1-6	.56	-.03

Legend: Higher scores represent higher levels of anxiety and depression.
Differences calculated with Mann-Whitney U test. Significant differences at p<.05 are presented in bold.
Abbreviations: HPN, home parenteral nutrition; IQR, interquartile range.

mothers of a healthy child (8.1% vs 25.3%, p = .02). Fathers reported significantly more problems on 9/34 everyday problems when their child was ≥2 years, or 8/36 everyday problems when their child was <2 years. Everyday problems on which both HPN mothers and fathers reported significantly more problems were: child care, leisure time, dealing with friends, interacting with child(ren), loneliness, concentration, independence of child, and following advice about treatment/giving medication.

Additional questions

When asked about support, people reacting with a lack of understanding, and parental chronic illness, HPN parents did not differ significantly from reference parents (Table 5a). HPN parents did indicate more often than reference parents (mothers: 40.5% vs 17.1%, p < .001, fathers: 33.3% vs 12.5%, p = .004) a possible wish to talk to a professional about their situation. About one third of HPN parents answered the open question (results not shown). The topics they brought up were very diverse; about the next appointment, financial issues regarding the care of their child on HPN, work, medical staff, emotional issues, and the wish to talk to a psychologist.

Table 5a. DT-P thermometer score, problem domain scores and additional questions in HPN mothers and fathers compared with reference groups of mothers and fathers of healthy children

	Mothers					Fathers				
	HPN (N=37)	Reference (N=671)	*p*	r / OR	95% CI	HPN (N=24)	Reference (N=463)	*p*	r / OR	95% CI
Thermometer score										
Median (IQR)	5 (3-7)	3 (1-6)	**.001**	-.13		3 (2-7)	2 (1-5)	**.03**	-.10	
Clinical, %	64.9	42.3	**.007**	2.50	1.27-5.00	45.8	32.2	.17	1.79	.78-4.00
Total problem score [a], Med (IQR)	6 (3-12.5)	4 (1-8)	**.006**	-.10		6 (1-9)	2 (1-5)	.13	-.07	
Practical problems, Med (IQR)	1 (0-3)	1 (0-2)	**.04**	-.08		1 (0-2)	0 (0-1)	.12	-.07	
Social problems, Med (IQR)	0 (0-1.5)	0 (0-1)	.09	-.06		0 (0-1)	0 (0-0)	**.002**	-.14	
Emotional problems, Med (IQR)	2 (.5-5)	1 (0-3)	**.005**	-.10		2 (0-4)	0 (0-2)	**.02**	-.11	
Physical problems, Med (IQR)	2 (1-3)	2 (0-3)	.42	-.04		1 (0-2)	1 (0-2)	.78	-.01	
Cognitive problems, Med (IQR)	0 (0-2)	0 (0-1)	**.02**	-.10		0 (0-1)	0 (0-0)	.14	-.07	
Parenting problems ≥2, Med (IQR) [b]	1 (0-2.5)	0 (0-0)	**.001**	-.21		1 (0-2)	0 (0-0)	**.000**	-.22	
Parenting problems <2, Med (IQR) [c]	0 (0-2)	0 (0-1)	.44	-.05		2 (0-2)	0 (0-1)	**.02**	-.24	
Additional questions										
Enough support from surroundings, %	91.1	92.1	1.00*	.97	.29-3.23	87.5	93.3	.23	.50	.14-1.79
People react with a lack of understanding, %	18.9	11.3	.16	1.82	.78-4.35	20.8	10.2	.10	2.33	.83-6.67
Parental chronic illness	10.8	20.3	.20	.48	.17-1.37	25.0	14.0	.14	2.04	.78-5.26
Would like to talk to a professional about situation - Yes/Maybe, %	40.5	17.1	**.000**	3.33	1.67-6.67	33.3	12.5	**.004**	3.45	1.43-8.33

Legend: Significant differences at $p < .05$ are presented in bold.
Domain scores: Mann-Whitney U-tests with effect sizes r, item scores: Chi^2 tests with OR and 95% CI
*=Fishers Exact (<N=5 in one cell)
a Total problem score = the sum of item scores (yes=1, no=0) within 5 problem domains (practical, social, emotional, physical and cognitive)
b N=25 HPN mothers, N=560 reference mothers, N=17 HPN fathers, N=370 reference fathers
c N=12 HPN mothers, N=111 reference mothers, N=7 HPN fathers, N=93 reference fathers
Abbreviations: CI, confidence interval; HPN, home parenteral nutrition; IQR, interquartile range; Med, median.

Table 5b. DT-P everyday problem scores of HPN mothers and fathers compared with reference groups of mothers and fathers of healthy children

	Mothers					Fathers				
	HPN (N=37)	Reference (N=671)	*p*	OR	95% CI	HPN (N=24)	Reference (N=463)	*p*	OR	95% CI
Practical problems										
Housing, %	10.8	5.5	2.63*	2.08	.70-6.25	4.2	3.7	.60*	1.14	.15-9.09
Work/study, %	8.1	25.3	**.02***	.26	.08-.85	25.0	25.9	.92	.95	.37-2.44
Finances/insurance, %	10.8	16.7	.49*	.61	.21-1.75	4.2	14.5	.23*	.26	.03-1.92
Housekeeping, %	35.1	21.6	.05	1.96	.98-4.00	20.8	12.1	.21	1.92	.68-5.26
Transport, %	8.1	4.6	.41*	1.82	.53-6.25	0.0	3.9	1. 00*	[c]	
Child care/child supervision, %	32.4	10.1	**.000**	4.17	2.04-9.09	16.7	5.4	**.047***	3.45	1.11-11.11
Leisure activities/relaxing, %	45.9	22.4	**.001**	2.94	1.52-5.88	54.2	14.9	**.000**	6.67	2.94-16.67
Social problems										
Dealing with (ex)partner, %	16.2	12.4	.49	1.37	.56-3.33	16.7	11.7	.51*	1.52	0.50-4.55
Dealing with family, %	16.2	10.9	.32	1.59	.64-3.85	4.2	6.7	1.00*	.61	0.08-4.55
Dealing with friends, %	13.5	3.7	**.004**	4.00	1.45-11.11	29.2	1.5	**.000**	25.00	8.33-100.00
Interacting with your child(ren), %	24.3	11.8	**.02**	2.38	1.10-5.26	25.0	7.8	**.003**	4.00	1.47-11.11
Emotional problems										
Controlling emotions, %	43.2	27.4	**.04**	2.00	1.03-4.00	25.0	11.9	.06	2.50	.94-6.67
Self-confidence, %	24.3	22.7	.81	1.10	.51-2.38	8.3	12.7	.76*	.62	.14-2.70
Fears, %	18.9	10.7	.12	1.92	.82-4.55	16.7	6.5	.08*	2.86	.93-9.09
Depression, %	43.2	31.9	.15	1.61	.83-3.23	45.8	22.2	**.008**	2.94	1.28-6.67
Feeling tense or nervous, %	54.1	36.1	**.03**	2.08	1.08-4.00	41.7	26.3	.10	2.00	.86-4.55
Loneliness, %	21.6	7.7	**.003**	3.23	1.43-7.69	20.8	3.7	**.000**	6.67	2.33-20.00
Feelings of guilt, %	24.3	17.4	.29	1.52	.70-3.33	16.7	7.3	.11*	2.50	.81-7.69
Use of substances (e.g. alcohol, drugs and/or medication) , %	5.4	2.7	.28*	2.08	.46-9.09	8.3	3.0	.18*	2.94	.63-14.29
Intrusive/recurrent thoughts about a specific event, %	43.2	20.4	**.001**	2.94	1.52-5.88	25.0	13.8	.13	2.08	.79-5.56

Table 5b. DT-P everyday problem scores of HPN mothers and fathers compared with reference groups of mothers and fathers of healthy children (continued)

	Mothers					Fathers				
	HPN (N=37)	Reference (N=671)	*p*	OR	95% CI	HPN (N=24)	Reference (N=463)	*p*	OR	95% CI
Physical problems										
Eating, %	5.4	12.4	.30*	.40	0.10-1.72	0.0	4.8	.62*	[c]	
Weight, %	27.0	26.2	.92	1.04	.50-2.17	4.2	16.6	.15*	.22	.03-1.64
Sleep, %	37.8	29.7	.29	1.45	.73-2.86	25.0	21.4	.67	1.22	.47-3.13
Fatigue, %	73.0	55.7	**.04**	2.13	1.02-4.55	50.0	44.1	.57	1.27	.56-2.86
Out of shape/condition, %	27.0	20.9	.37	1.41	.66-2.94	25.0	19.0	.47	1.43	.55-3.70
Pain, %	24.3	24.3	.99	1.00	.46-2.17	4.2	18.1	.10*	.20	.03-1.47
Sexuality, %	8.1	10.6	.79*	.75	.22-2.50	8.3	8.9	1.00*	.93	.21-4.17
Cognitive problems										
Concentration, %	35.1	17.9	**.009**	2.50	1.23-5.00	29.2	11.2	**.009**	3.23	1.28-8.33
Memory, %	40.5	22.4	**.01**	2.38	1.20-4.76	20.8	13.6	.32	1.67	.60-4.55
Parenting problems ≥2 [a]										
Dealing with your child, %	8.0	10.9	1.00*	0.02	.16-3.13	11.8	9.7	.68*	1.23	.27-5.56
Dealing with the feelings of your child, %	44.0	9.3	**.000**	7.69	3.33-16.67	17.6	8.6	.19*	2.27	.62-8.33
Talking about the disease/consequences with your child, %	20.0	3.0	**.000**	7.69	2.70-25.00	11.8	2.7	.09*	4.76	.96-25.00
Independence of your child, %	48.0	7.5	**.000**	11.11	4.76-25.00	23.5	7.6	**.04***	3.70	1.15-12.50
Following advice about treatment/giving medication, %	20.0	3.4	**.000**	7.14	2.44-20.00	41.2	3.0	**.000**	25.00	7.14-100.00
Parenting problems <2 [b]										
Feeling connected with your child	0.0	1.8	1.00*	[c]		14.3	1.1	.14*	14.29	.85-250
Caring for your child	16.7	1.8	**.047***	11.11	1.39-100.00	0.0	3.2	1.00*	[c]	
Feeding your child	25.0	17.1	.45	1.61	.40-6.67	42.9	9.7	**.04***	7.14	1.35-33.33
Development of your child	8.3	7.2	1.00*	1.18	.13-10.00	28.6	4.3	.06*	9.09	1.30-50.00

Table 5b. DT-P everyday problem scores of HPN mothers and fathers compared with reference groups of mothers and fathers of healthy children (continued)

	Mothers					Fathers				
	HPN (N=37)	**Reference (N=671)**	***p***	**OR**	**95% CI**	**HPN (N=24)**	**Reference (N=463)**	***p***	**OR**	**95% CI**
Following advice about treatment/giving medication, %	8.3	2.7	.34*	3.23	.31-33.33	14.3	1.1	.14*	14.29	0.85-250
Your child's sleeping	33.3	23.4	.48*	1.64	.45-5.88	28.6	20.4	.64*	1.56	.28-8.33
Behavior/crying of your child	16.7	16.2	1.00*	1.03	.21-5.00	14.3	17.2	1.00*	0.08	.09-7.14

Legend: Significant differences at p < .05 are presented in bold. Item scores: Chi-square tests with OR and 95% CI
*=Fishers Exact (<N=5 in one cell)
a N=25 HPN mothers, N=560 reference mothers, N=17 HPN fathers, N=370 reference fathers
b N=12 HPN mothers, N=111 reference mothers, N=7 HPN fathers, N=93 reference fathers
c When N=0 in HPN parents, OR cannot be calculated
Abbreviations: CI, confidence interval; HPN, home parenteral nutrition; OR, odds ratio.

DISCUSSION

This study compared mothers and fathers of children dependent on HPN with reference parents. On most subscales of the HRQOL questionnaire, no significant differences were found between both groups. Fathers only reported more problems on the subscale daily activities, and mothers on the subscale depressive emotions. On the anxiety and depression questionnaire, HPN mothers also showed higher mean levels of depression. However, when comparing proportions of mothers and fathers scoring in the clinical range, no significant differences were found between HPN parents and reference parents. Regarding overall parental distress, both HPN mothers and fathers did report significantly higher levels than reference parents.

An unexpected result of our study is that only small differences were found on HRQOL, with quite small effect sizes. A large study in parents of children with various chronic conditions, such as asthma or metabolic disease, using the same questionnaire and reference group, did show lower scores on HRQOL.[21] An explanation might be that, for the HPN parents, practical everyday problems are more prominent, as shown in the DT-P results, rather than general HRQOL. Parents might also adjust their expectations after taking care of a child with a chronic illness for a long time. Qualitative research might give more insight into these processes. Similar results were found in a recent study in parents of children with Down's syndrome, implying that asking about distress in general is not sufficient and healthcare professionals should address or ask about specific problems.[28]

Specific problems that were reported by mothers as well as by fathers, e.g. dealing with friends, may represent relevant everyday problems in these families. This example is consistent with earlier findings[7], where HPN parents did not differ from the normal population on overall social interaction, but showed a different pattern in the subscales. Superficial and simple social contacts were high, whereas deeper, emotional relations were affected. In addition, in the current study, HPN parents reported problems with the independence of their child, loneliness and leisure time. This corresponds with results of another qualitative study in HPN patients and their parents, where isolation, e.g. finding a source of support, was a major theme[15], and also with the results of another Dutch study, which showed that parents of chronically ill children spent less time doing leisure activities.[29] Although HPN parents in this study did not report more problems with their (ex)partner than reference parents, and the vast majority of the parents is married/living together, it is important to pay attention to the quality of the partner relation in clinical practice. This is shown in research within parents of children with Down's syndrome, where fathers also did not report more problems with their (ex)partner, measured with the same DT-P questionnaire[28], but the same fathers did indicate a worse partner relation (marital satisfaction, conflict-management, support and trust) on another questionnaire.[30]

Furthermore, our findings reflect the results of a small survey[31], which indicated that almost all HPN families experienced great difficulty trying to find a person to look after their child and going out. Sleep disturbance was common for parents, as they had to attend to the equipment and their child at night. Many families experienced deterioration in their family life, i.e. social activities, and overall quality of life after their child started HPN. Although families coped well with HPN, they frequently suffered from social isolation.[31]

A striking finding is that HPN mothers report less problems regarding work/study than reference mothers. An explanation may be that the majority of the HPN mothers in our cohort do not have paid employment (Table 2), consistent with the earlier finding that mothers of chronically ill children work fewer hours a week.[29] However, it may also reflect a tendency to choose for a less demanding career, to combine work with the care for their child, as found in a previous study on parents of children with Down's syndrome.[32]

Previous research showed that fear, frustration, and anger were frequently expressed negative feelings of HPN mothers.[15] The initial experience of being discharged with a child receiving PN was terrifying. However, HPN was seen as lifesaving and miraculous. Mothers expressed being overwhelmed with so much to learn at initiation of HPN. This does not reflect our findings, since both on the anxiety scale of the HADS as the item 'fears' on the DT-P, parents did not show significantly elevated scores compared to reference parents. This could be explained by the fact that children of the parents in this study were receiving HPN on average for over 3 years already, and the initial stress after the start of HPN might be reduced. This also reflects previous findings, where longer time intervals since hospitalization were associated with lower parental stress levels.[10]

The current study is the first that systematically inquired about HRQOL, anxiety, depression, distress and everyday problems in both HPN mothers and fathers, and used reference groups. Although the number of participants might seem small, almost all parents of children on HPN in the Netherlands were approached to participate, as the centers in Amsterdam and Rotterdam treat the majority of Dutch pediatric HPN patients. Although participants and non-participants could not be compared on all characteristics, with the high response rate, our results can be seen as representative for the Dutch population of HPN parents.

Our study does, however, have some limitations. In this study, parents completed the questionnaires on the KLIK website in order to discuss the answers with the healthcare professional, who could see the answers, during the outpatient consultation. This is part of standard care to identify problems at an early stage and to see how parents and patients are doing longitudinally. Parents in all three reference groups completed the questionnaires anonymously. The effect of the difference between anonymous and

non-anonymised responses is unknown. One might hypothesize that parents who do not complete questionnaires anonymously, report less problems than they in reality experience, because some parents do not want their answers to be discussed, or social acceptability is at stake. In that case, the difference in this study between HPN parents and reference groups might be bigger. Another limitation is that we do not know whether parents in our study already received psychosocial help. Therefore, the question about wanting to talk to a professional needs to be interpreted with caution.

Future research could be directed at potential risk- and protective factors of psychosocial functioning, e.g. socio-economic, medical factors (such as number of nights the child is on HPN), coping and social support, in order to detect and support the parents who are at risk for impaired psychosocial functioning at an early stage. Also, longitudinal studies to follow these parents would be interesting, for example to see if most parents are still married/living together and how this may affect their psychosocial wellbeing. Additionally, to be able to compare outcomes on how these parents are doing, the use of the same outcomes and questionnaires is needed in international studies. In addition, qualitative research, using semi-structured interviews, can give more insight into the (HPN) specific problems parents may experience, not captured by the three questionnaires in this study.

In conclusion, although the HRQOL of HPN parents is only affected on one subscale of the TAAQOL for mothers, and on one for fathers, some parents experience high levels of parental distress and everyday problems. The results stress the importance of implementing structured parental psychosocial screening in daily clinical practice. In the Netherlands, HPN mothers and fathers complete the DT-P on the KLIK website once a year. Therefore, annual screening of Dutch HPN parents is warranted. The aim of using a screening questionnaire such as the DT-P is an early identification of psychosocial problems. Parents can also use this questionnaire to ask the multidisciplinary team for additional practical or psychosocial support. After identifying which parents want and need support, referrals to a social worker or psychologist should be made and tailor-made interventions could be provided. Practically, it is possible to receive homecare, including overnight support, for Dutch children dependent on HPN and their families. Parents receive a personal budget from the health insurance company, to hire nurses for homecare or other assistance, for example support at the school of their child. Psychosocially, interventions aimed at reducing depressive symptoms could be offered. A previous review also recommends that individual healthcare plans should include a strong psychosocial component to assess ongoing family needs[31]. Families must be encouraged to identify what kind of help they require.[31] With structural screening of parental psychosocial problems, the well-being of both these parents and their children dependent on HPN can be improved.

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PART II

ORGANIZATIONAL ASPECTS

9

Presentation of a nationwide multicenter Registry of Intestinal Failure and Intestinal Transplantation

Clin Nutr. 2016 Feb;35(1):225-9.

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ABSTRACT

Background & aims

Exact data on Dutch patients with chronic intestinal failure (CIF) and after intestinal transplantation (ITx) have been lacking. To improve standard care of these patients, a nationwide collaboration has been established. Objectives of this study were obtaining an up-to-date prevalence of CIF and characterizing these patients using the specially developed multicenter web-based Dutch Registry of Intestinal Failure and Intestinal Transplantation (DRIFT).

Methods

Cross-sectional study. CIF was defined as type 3 intestinal failure in which >75% of nutritional requirements were given as home parenteral nutrition (HPN) for ≥ 4 weeks in children and > 50% for ≥ 3 months in adults. All patients with CIF receiving HPN care by the three Dutch specialized centers on January 1, 2013 and all ITx patients were registered in DRIFT (https://drift.darmfalen.nl).

Results

In total, 195 patients with CIF (158 adults, 37 children) were identified, of whom 184 were registered in DRIFT. The Dutch point prevalence of CIF was 11.62 per million (12.24 for adults, 9.56 for children) on January 1, 2013. Fifty-seven patients (31%) had one or more indications for ITx, while 12 patients actually underwent ITx since its Dutch introduction. Four patients required transplantectomy of their intestinal graft and 3 intestinal transplant patients died.

Conclusion

The multicenter registry DRIFT revealed an up-to-date prevalence of CIF and provided nationwide insight into the patients with CIF during HPN and after ITx in the Netherlands. DRIFT will facilitate the multicenter monitoring of individual patients, thereby supporting multidisciplinary care and decision-making.

INTRODUCTION

Intestinal failure (IF) is characterized by the inability to maintain protein-energy, fluid, electrolyte and/or micronutrient balance, resulting from anatomic reduction or functional failure of the gut.[1] Patients with chronic and/or irreversible IF (CIF) depend on parenteral nutrition (PN) to survive, which can be provided at home. Home parenteral nutrition (HPN) is rare with a European prevalence ranging from 2-40 per million in adults[2] and 0.34-8.92 in children.[3] The treatment of IF requires a multidisciplinary approach which includes members specialized in (pediatric) surgery, (pediatric) gastroenterology, dieticians and nurse specialists. Intestinal transplantation (ITx) has become an alternative for patients with life-threatening complications of PN. Due to the lower survival rates after intestinal transplantation (ITx) than on HPN, HPN is still the treatment of choice.

A good collaboration between centers for HPN and transplant centers is the cornerstone of the management of patients with CIF. It has been shown that early referral to the transplant center is related to higher survival.[4] However, the optimal timing to refer is difficult to determine by caregivers in HPN centers, while the exact medical status including detailed documentation of complications is often unclear to the transplant professionals. To improve standard care of these patients, a nationwide collaboration has been established. The last registration of patients with CIF in the Netherlands has been performed in 2004, with a prevalence of long-term PN of at least 5.1 per million adults and 0.6 per million children.[5] An up-to-date registration including an actual overview of the individual patient is therefore necessary. For this purpose the web-based Dutch Registry of Intestinal Failure and Transplantation (DRIFT) was developed. The objectives of this study were to obtain an up-to-date prevalence of CIF and to characterize the Dutch patients with CIF and after ITx by using the multicenter registry DRIFT.

METHODS

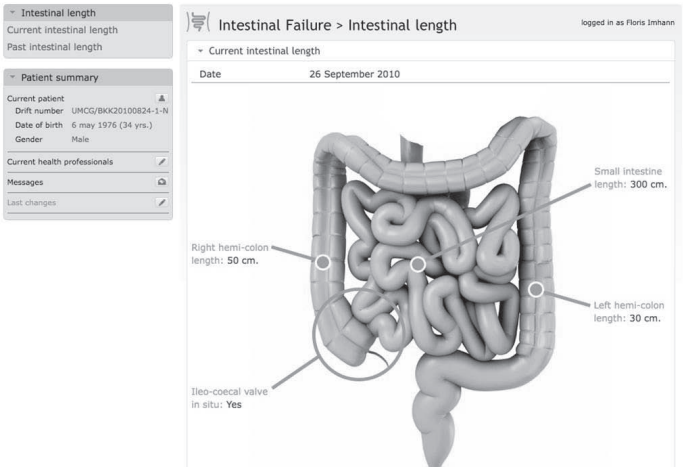
Study design

HPN care in the Netherlands is coordinated by three specialized centers, located in Amsterdam (Academic Medical Center) and Nijmegen (Radboud University Medical Center) for adults and children and in Rotterdam (Erasmus Medical Center - Sophia Children's Hospital) for children only. Adults and children with CIF receiving HPN care provided by these centers on January 1, 2013 were included in DRIFT. Patients from Maastricht University Medical Center were only taken into account for the calculation of the Dutch CIF prevalence, since this center does not participate in the nationwide collaboration because of geographical reasons. CIF was defined as type 3 IF: chronic IF requiring long-term nutritional support in the form of HPN.[6] We specified this adding that > 75% of nutritional requirements had to be given as HPN for ≥ 4 weeks in children (in line with the definition of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)) and > 50% for ≥3 months in adults.[7] Patients who were receiving HPN in the absence of IF or as a bridge to a gastrointestinal continuity procedure were excluded. All patients who underwent ITx in the single Dutch transplant center (University Medical Center Groningen) were included.

Data collection & registration

Data for this cross-sectional study were obtained using medical patient records. Data known on January 1, 2013 were registered in DRIFT. This registry is available online in English at https://drift.darmfalen.nl (see supplement). **Figure 1** shows how data are displayed in DRIFT. Patient safety was ensured according to ISO-27001 and Dutch Data Protection Act standards.

Figure 1. DRIFT



Data definitions

- Catheter-related bloodstream infection (CRBSI) was defined as a positive central venous catheter (CVC) blood culture or positive peripheral blood culture in patients who met the clinical criteria of sepsis, while another focus was highly unlikely.
- Critical loss of vascular access was defined as occlusion of ≥2 from the 4 primary veins (jugular and subclavian) for the placement of a vascular access, confirmed by ultrasound or phlebography.[7]
- We used total bilirubin (along with information of the last hepatic ultrasound and liver biopsy) as documented at last follow-up to assess liver dysfunction, since this value is also used in the ITx criteria. Patients who were clinically unstable or with liver dysfunction unrelated to PN were excluded for the analysis.
- Potential ITx candidates were identified using the indications defined by the USA Center for Medicare and Medicaid Services[8] and the American Society of Transplantation.[9] We specified the definitions of pending liver dysfunction (total bilirubin > 50 μmol/L), overt liver failure (signs of portal hypertension, liver fibrosis or cirrhosis) and CIF with high morbidity (≥3 hospitalizations per year, with each a minimal duration of 7 days) since the description of these indications could be interpreted in various ways (supplementary **Table 1**).

Statistics

Patients were categorized in two groups, adults (≥ 18 years) and children (< 18 years). The national point prevalence was calculated from the latest estimate for the population in the Netherlands (Statistics Netherlands). Data were described as mean and standard deviation (if distributed normally) and median and range (if not distributed normally) it continuous and absolute frequencies and percentages if categorical. Analyses were performed using SPSS version 20 for Windows (IBM, Armonk, NY, USA).

RESULTS

In total, 195 Dutch CIF patients (158 adults and 37 children) were identified (supplementary **Figure 2**). This provides a point prevalence of 11.62 per million (12.24 for adults, 9.56 for children) on January 1, 2013.

Patient characteristics of the 184 patients included in DRIFT are presented in **Table 2**. Fifty-seven patients (31%, 39 adults and 18 children) had one or more indications for ITx (supplementary **Table 3**). Since 2001, 12 patients underwent ITx (**Table 4**). Indication for ITx was insufficient vascular access due to CVC-related thrombosis of ≥ 2 central veins in 5 patients, frequent CVC-related sepsis (2 patients), liver failure (2 patients), insufficient vascular access and frequent CVC-related sepsis combined (1 patient), frequent CVC-related sepsis and a depressed quality of life combined (1 patient) and depressed quality of life (1 patient). The indication for a combined small bowel and kidney transplantation was pre-emptive in 2 patients and chronic renal failure due to post-infectious glomerulonephritis in the third patient. Four patients (33.3%) suffered from severe rejection requiring transplantectomy of the intestinal graft after a median time of 8.56 months (range 2.33 – 23.00). Three patients died because of sepsis, euthanasia and massive psoas bleeding after a median time of 23.89 months (range 15.11 – 35.98). There were no patients on the waiting list for ITx on January 1, 2013.

Table 2. Patient characteristics of adults and children with chronic intestinal failure (CIF) receiving home parenteral nutrition (HPN) on January 1, 2013 (data excludes patients from Maastricht)

		Adults (n = 147)	Children (n = 37)
Gender	N (%)		
Female		102 (69.4)	14 (37.8)
Male		45 (30.6)	23 (62.2)
Cause of intestinal failure	N (%)		
Short bowel syndrome		75 (51.0)	14 (37.8)
Motility disorder		57 (38.8)	15 (40.5)
Enteropathy		8 (5.4)	6 (16.2)
Combined*		7 (4,8)	2 (5.4)
Underlying disease	N (%)		
Motility disorder other than CIPO		41 (27.9)	3 (8.1)
Inflammatory bowel disease		25 (17.0)	0 (0)
Ischemic bowel		29 (19.7)	0 (0)
Tumor		11 (7.5)	0 (0)
CIPO		11 (7.5)	11 (29.7)
Radiation enteritis		9 (6.1)	0 (0)
Adhesions/fistulas		9 (6.1)	0 (0)
Volvulus/malrotation/mechanical obstruction		8 (5.4)	3 (8.1)

Table 2. Patient characteristics of adults and children with chronic intestinal failure (CIF) receiving home parenteral nutrition (HPN) on January 1, 2013 (data excludes patients from Maastricht) (continued)

		Adults (n = 147)	Children (n = 37)
Trauma		2 (1.4)	0 (0)
Graft versus host disease		2 (1.4)	0 (0)
Necrotizing enterocolitis		0 (0)	5 (13.5)
Microvillus inclusion disease		0 (0)	4 (10.8)
Gastroschisis		0 (0)	3 (8.1)
Intestinal atresia		0 (0)	3 (8.1)
Meconium ileus		0 (0)	1 (2.7)
Long gap oesophageal atresia		0 (0)	1 (2.7)
Congenital absorption disorder		0 (0)	2 (5.4)
Cloacal exstrophy		0 (0)	1 (2.7)
Age at January 1, 2013	Median (range), years	54.04 (18.04 – 78.67)	3.82 (0.35 – 16.95)
Age at start PN	Median (range), years	49.23 (7.11 – 75.77)	0.04 (0.00 – 11.90)
Duration on PN	Median (range), years		
General		2.92 (0.28 – 36.42)	3.04 (0.35 – 11.97)
Short bowel syndrome		3.25 (0.36 – 36.42)	2.62 (0.36 – 9.54)
Motility disorder		2.92 (0.28 – 19.50)	3.82 (0.35 – 11.97)
Enteropathy		1.18 (0.44 – 4.92)	2.96 (1.55 – 8.88)
Combined*		2.39 (0.96 – 11.09)	4.58 (3.13 – 6.03)
Duration on PN	N (%)		
< 1 year		32 (21.8)	6 (16.2)
1 – 5 years		70 (47.6)	21 (56.8)
5 – 10 years		27 (18.4)	9 (24.3)
10 – 20 years		14 (9.5)	1 (2.7)
> 20 years		4 (2.7)	-
Remaining small bowel			
Whole small bowel in situ	N (%)	56 (38.1)	17 (45.9)
≥ 1 small bowel resections	N (%)	91 (61.9)	20 (54.1)
Small bowel length documented	N (%)	64 (70.3)	15 (75.0)
Small bowel length	Median (range), cm	70.00 (0 – 250)	32.00 (5 – 90)
≤ 50 cm		26 (40.6)	10 (66.7)
50 - 100 cm		18 (28.1)	5 (33.3)
100 - 200 cm		19 (29.7)	0 (0)
200 - 300 cm		1 (1.6)	0 (0)
Colon in continuity			
Yes		47 (51.6)	14 (70.0)
No		44 (48.4)	6 (30.0)
Presence of ileocoecal valve	N (%)		
Yes		63 (42.9)	25 (67.6)
No		76 (51.7)	12 (32.4)

Table 2. Patient characteristics of adults and children with chronic intestinal failure (CIF) receiving home parenteral nutrition (HPN) on January 1, 2013 (data excludes patients from Maastricht) (continued)

		Adults (n = 147)	Children (n = 37)
Unknown		8 (5.4)	0 (0)
Stoma	N (%)		
Jejuno- or ileostomy		59 (40.1)	7 (18.9)
Colostomy		10 (6.8)	1 (2.7)

Legend: * Combination of short bowel syndrome and motility disorder or enteropathy.
Abbreviations: CIPO, chronic intestinal pseudo-obstruction; PN, parenteral nutrition.

Table 4. Characteristics of patients who underwent intestinal transplantation (ITx)

		Adults (n = 7)	Children (n = 5)
Gender	N		
Female		6	1
Male		1	4
Type of intestinal failure	N		
Short bowel syndrome		6	1
Motility disorder		1	1
Enteropathy			3
Underlying disease	N		
Mesenteric artery thrombosis		5	-
Microvillus inclusion disease		-	2
Chronic intestinal pseudo-obstruction		1	-
Volvulus		-	1
Total aganglionosis		-	1
Complicated surgery		1	-
Absorption disorder not specified		-	1
Duration on PN	Median, range (years)	6.21 (0.85 – 15.24)[a]	4.59 (2.50 – 5.46)
Age at ITx	Median, range (years)	43.05 (35.50 – 54.64)	4.80 (2.50 – 5.46)
Type of ITx	N		
Isolated		4	3
Small bowel with kidney		4[a]	-
Combined liver-small bowel		-	2
Outcome	N		
Alive with functioning graft		4[a]	2
Alive without functioning graft		1	2
Deceased		2	1

Legend: [a] One patient underwent re-transplantation (after 0.85 years on parenteral nutrition).
Abbreviations: ITx, intestinal transplantation; PN, parenteral nutrition.

DISCUSSION

This report presents the web-based registry DRIFT and describes the first results of registration of patients with CIF and patients after ITx in the Netherlands. To improve standard care of these patients, a nationwide collaboration has been established. To facilitate this nationwide collaboration, up-to-date data on Dutch patients with CIF and after ITx were necessary. Until the development of DRIFT, these data have been lacking. DRIFT has a multicenter and multidisciplinary nature, since both patients receiving HPN and after ITx in different centers can be registered. As far as we know, such a nationwide multicenter and multidisciplinary registry has not been described before. Registration in DRIFT has provided a point prevalence of CIF of 11.62/million inhabitants on January 1, 2013. The increase in CIF patients with HPN[2,5] might reflect both increasing numbers of patients and increased experience in specialized HPN centers with improvement of overall HPN survival rates. However, previous insufficient documentation might be partially responsible as well. Comparing this prevalence with other countries is difficult since different definitions of CIF and indications for HPN are used. In the Netherlands, patients with end-stage cancer rarely receive HPN, in contrast to the United States and Mediterranean countries, where the prevalence of HPN in those cases is higher.[5,10] However, the Dutch CIF-patient population seems similar to populations reported in Europe, Canada and earlier Dutch reports.[2,5]

Thirty-one percent of the CIF patients receiving HPN met the criteria for screening for ITx. The discrepancy with the number of patients who actually underwent ITx in the Netherlands is explained by the conscious and cautious-restrictive policy in the Dutch transplant center. This policy is based on the current superiority of HPN care over ITx in the Netherlands. However, this discrepancy suggests also that an update of the indications for ITx is necessary, as has been indicated by other professionals in the field.[11] With DRIFT, these vulnerable patients can be monitored closely in order to decide whether they should be referred to the transplant center or not.

One of the limitations of this study is that we chose to apply a strict definition in line with definitions earlier described by Lal et al.[6], Beath et al.[7] and ESPGHAN, which might have led to an underestimation of the prevalence of CIF and HPN. We expect that some of the 41 patients that did not meet the criteria for CIF on January 1, 2013, will not be able to wean from HPN and therefore deserve to be included. Furthermore, data were incomplete for some patients, because information was not available or specific measurements had not been performed.

In conclusion, the novel, English language web-based registry DRIFT provided an up-to-date prevalence of CIF and a nationwide insight into patients with CIF during HPN and after ITx in the Netherlands. DRIFT will facilitate the monitoring of individual patients by

functioning as a national Electronic Patient Register (EPR), thereby supporting multidisciplinary care and decision-making in this clinically complex patient population. DRIFT will be used as a quality instrument between the different Dutch centers. Our aim is to extend this registry to other countries.

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SUPPLEMENTARY MATERIAL

Table 1. Indications to identify potential intestinal transplantation (ITx) candidates in our population of patients with chronic intestinal failure (CIF) on home parenteral nutrition (HPN)

Indications[8,9]
Failure of HPN
- Insufficient vascular access due to CVC-related thrombosis of ≥ 2 central veins (subclavian or jugular veins)
- Frequent (≥ 2/year) episodes of CRBSI
- Liver dysfunction
Pending:
-Total bilirubin > 50 µmol/l
Overt: - ≥ 1 of the following criteria;
- Signs of portal hypertension
- Liver fibrosis or cirrhosis
High risk of death attributable to underlying disease
Intra-abdominal invasive desmoid tumours
Congenital enteropathy
Ultra-short bowel syndrome (gastrostomy, duodenostomy, remaining small bowel length < 10 cm in children and < 20 cm in adults)
CIF with high morbidity
Need for frequent hospitalization because of HPN related complications (≥3 hospitalizations per year, with each a minimal duration of 7 days)
Severe impairment of Quality of Life (disregarded in this research)

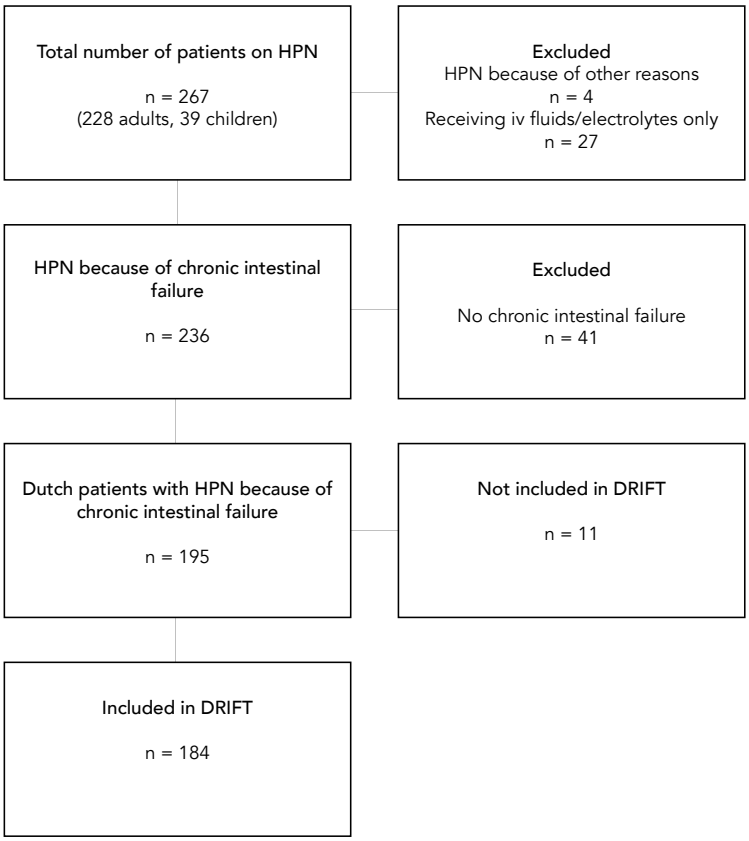
Abbreviations: CRBSI, catheter-related bloodstream infection; CVC, central venous catheter.

Table 3. Identification of potential intestinal transplantation (ITx) candidates

Indication (n, (%))	**Patients (n = 184)**	**Adults (n = 147)**	**Children (n = 37)**
Treatment failure of HPN			
Insufficient vascular access	10 (5.4)	8 (5.4)	2 (5.4)
Liver dysfunction			
Pending	5 (2.7)	5 (3.4)	0 (0.0)
Overt	17 (9.2)	10 (6.8)	7 (18.9)
Splenomegaly	14 (7.6)	9 (6.1)	5 (13.5)
Splenomegaly with ascites	3 (1.6)	1 (0.7)	2 (5.4)
Fibrosis/cirrhosis	0 (0)	0 (0)	0 (0)
Frequent CRBSI	32 (17.4)	24 (16.3)	8 (21.6)
High risk of death attributable to underlying disease			
Desmoid tumor	1 (0.5)	1 (0.7)	0 (0.0)
Congenital enteropathy	6 (3.3)	0 (0)	6 (16.2)
Ultra-short bowel syndrome	15 (8.2)	12 (8.2)	3 (8.1)
CIF with high morbidity			
≥ 3 hospitalizations per year	5 (2.7)	2 (1.4)	3 (8.1)
Total	57 (31.0)	39 (26.5)	18 (48.6)

Abbreviations: CIF, chronic intestinal failure; CRBSI, catheter-related bloodstream infection; HPN, home parenteral nutrition.

Figure 2. Patient inclusion flowchart



Abbreviation: HPN, home parenteral nutrition.

10

Intestinal rehabilitation for children with intestinal failure is cost-effective: a simulation study

Am J Clin Nutr. 2017 Feb;105(2):417-425.

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ABSTRACT

Background

Children with intestinal failure (IF) depend on parenteral nutrition (PN). The goal in the treatment of IF is to wean children off PN through intestinal rehabilitation (IR). Although the healthcare burden of IF is enormous, to our knowledge there has been no previous cost-effectiveness analysis in pediatric IF including IR.

Objective

We sought to determine the cost-effectiveness of IR in terms of costs and life-years.

Design

We simulated the treatment of IF in children in a discrete-event model. Data for this model were derived from patient records, the Dutch Registry of Intestinal Failure and Transplantation, the Intestinal Transplant Registry, and the literature. The time horizon of the model was 40 y. Simulated patients were enrolled at a rate of 40 patients/mo for 10 y. Actual costs were calculated for hospital admissions, surgical interventions, endoscopies, PN, and immunosuppressive medication. We evaluated the cost-effectiveness of IR by comparing 1 scenario with IR with 1 scenario without IR. In the scenario with IR, a proportion of patients who represented those with the ability to wean off PN were assigned to IR. In the scenario without IR, all patients progressed to home PN (HPN). In both scenarios, a proportion of patients receiving HPN were eventually eligible for an intestinal transplantation.

Results

IR prolonged survival; the mean number of life-years per patient was 19.4 in the scenario with IR compared with 18.2 in the scenario without IR. Average total costs per patient were €819,292 in the scenario with IR compared with €1,176,830 in the scenario without IR (equivalent to 1,129,230 US$ and 1,622,025 US$, respectively, in January 2014); costs mainly included hospital admissions and PN.

Conclusion

On the basis of our simulations, we concluded that IR improved the survival of children with IF and was associated with cost savings. Therefore, we consider IR to be a cost-effective treatment for children with IF.

INTRODUCTION

Intestinal failure (IF) in children is defined as a critical reduction of the gut mass or its function below the minimum level necessary for the absorption of nutrients that are required to grow and develop.[1] The most common cause of IF in children is short bowel syndrome (SBS). IF can be reversible but this depends on factors such as the underlying disease and length of the remaining small bowel. Chronic or irreversible IF is rare with a reported prevalence of 9.56/1 million Dutch children.[2] To maintain adequate growth and nutritional status during IF, parenteral nutrition (PN) is necessary. In the case of chronic or irreversible IF, PN can be provided at home (home PN, HPN). However, PN can be complicated by serious and possibly life-threatening complications, including liver disease and catheter-related sepsis.[3] Therefore, intestinal rehabilitation (IR) is the accepted treatment strategy with the aim of weaning patients off of PN. IR consists of a systematic approach to stimulate the adaptation of the small bowel and includes the optimization of parenteral, enteral, and oral feeding, while maintaining growth, preventing eating disorders and complications, and maintaining a good quality of life (QoL).[4] For patients with life-threatening complications that are due to PN, an option is intestinal transplantation (ITx).[5] However, ITx is not the initial therapeutic choice because survival rates after ITx are lower than those achieved on PN.[6-8]

The care of patients with IF is complex and requires prolonged hospital admissions, multiple surgical procedures, frequent outpatient visits, and specialized nutritional support. Therefore, from a socioeconomic perspective, the healthcare burden of IF is enormous. Estimated annual HPN costs have differed widely, ranging between 75,000 and 290,000 US$/patient in 2006.[9] IR is also expensive and might not always be successful. A Dutch study reported an average total cost of €269,700 (including follow-up) in 2010 for infants with SBS, which mainly compromised the costs of hospital admissions.[10] In 2008, Spencer et al.[11] reported average total costs of care for children with SBS during the first 5 y of >1.6 million US$. Studies that investigated the costs of ITx in the United States (in 2006 and 2011) have reported that, on average, an isolated small-bowel transplantation costs 135,000 US$.[9,12] These high costs may be partly explained by late referrals to expert centers and a limited implementation of successful practices such as the use of taurolidine locks to prevent catheter-related sepsis.

Thus, pediatric IF is a major clinical problem in terms of morbidity, and it is associated with high costs. Still, little is known about the cost-effectiveness of IF treatment. A British cost-effectiveness analysis of ITx in children revealed conflicting results, and therefore, no firm conclusions could be drawn.[13] A recent Dutch cost-effectiveness study of ITx in adults showed that ITx improved the life-years of adults with irreversible IF for relatively low costs.[14] To our knowledge, there has been no previous comprehensive cost-

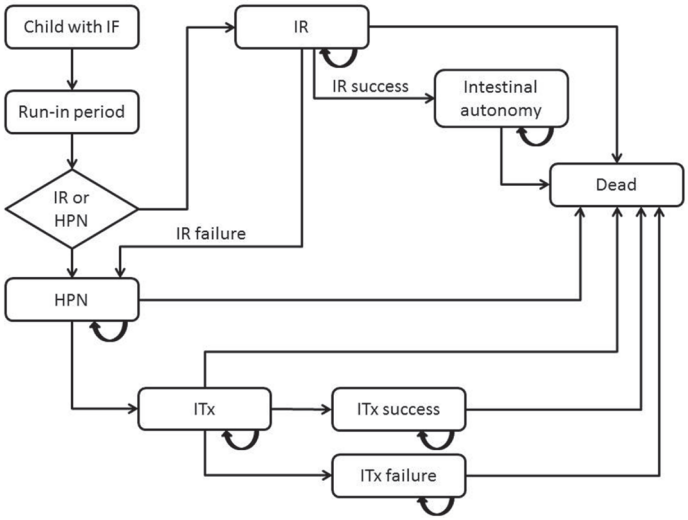
effectiveness analysis in pediatric IF including rehabilitation. On the basis of the results of IR, especially in terms of intestinal autonomy[4,15], it may be instinctively assumed that IR is a cost-effective treatment option. However, this assumption needs to be substantiated by evidence if IR wants to make a legitimate claim on scarce healthcare resources. Therefore, the purpose of this study was to estimate the cost-effectiveness of IR.

METHODS

Discrete event model

We simulated the treatment of IF in children in a discrete-event simulation model. Within such a model, patients move through the model experiencing events at any discrete time period after the previous event. Models such as these may be used to extrapolate costs and outcomes beyond the follow-up of clinical trials.[16,17] As shown by the graphical illustration of our model (**Figure 1**), the clinical course of patients was represented as a series of consecutive steps or states. On the basis of a similar model of ITx in adults[14], the clinical states included in the model were HPN, intestinal autonomy (successful IR), graft failure, and sustained graft function, whereas death was the final outcome. We modeled 2 scenarios; 1 scenario included the possibility of IR, and 1 scenario was modeled without IR. In the scenario with IR, a proportion of patients who represented those with the ability to wean off PN were assigned to IR, which could be successful (progression to intestinal autonomy) or unsuccessful. Patients who could not be weaned off PN progressed to HPN. In addition, all patients who did not have the ability to wean off PN from the start because of irreversible IF (e.g., because of an enteropathy) were assigned to the HPN

Figure 1. States (boxes) and transitions (arrows) in the simulation model consisting of IR, HPN, and ITx



Legend: The model started with a run-n period; all patients received a few days of PN before they were assigned to HPN or IR. In the scenario with IR, a patient with the ability to wean off PN was assigned to IR. IR could have been successful and lead to intestinal autonomy or unsuccessful (IR failure). In the latter case, patients progressed to HPN. In addition, patients who did not have the ability to wean off PN from the start because of irreversible IF were assigned to the HPN state. When ITx was indicated, patients were moved to receive an ITx. The ITx could have been successful or unsuccessful (ITx failure). Curved arrows indicate that patients could have remained in a certain state for multiple units of time.

Abbreviations: HPN, home parenteral nutrition; IF, intestinal failure; IR, intestinal rehabilitation; ITx, intestinal transplantation.

state. In both scenarios, a proportion of patients receiving HPN were eventually eligible for ITx. Patients were included immediately from the onset of IF while in the hospital. All children were dependent on PN for at least a few months.

Treatment choices were modeled by fixed probabilities or by comparing multiple time-dependent probabilities. The amount of time that simulated patients remained in each treatment state (transition time) was determined with the use of probabilistic Weibull functions, on the basis of the available data. The value for the duration in each treatment state for each individual patient was randomly drawn from the distribution of the associated Weibull function. In case of multiple possible outcomes, transition times were determined independently for each outcome, and the outcome associated with the shortest time was chosen. The time horizon of the model was 40 y. Half-cycle adjustment was applied to all counts that were generated by the model. To produce stable outcomes, the model was replicated 500 times. In each replication, all outcomes were calculated for the entire cohort of included patients. The model was constructed with the use of AnyLogic modeling software (version 7; AnyLogic Co.).

Model variables

Data for our model were obtained from patient records, the Dutch Registry of Intestinal Failure and Transplantation, the Intestinal Transplant Registry, expert opinions, and the literature (**Table 1**). In the Netherlands, the University Medical Center Groningen is the national center for ITx. HPN for children is provided by 3 specialized teams who are located in the Children's Hospitals of Amsterdam Medical Center, Erasmus Medical Center, and Radboud University Medical Center. IR is provided by these centers and the University Medical Center Groningen.

The number of new children with IF in the Netherlands was estimated at 15-20 individuals/y. However, we performed the simulations with an enrollment of 40 patients/mo as comparable with a multi-country population. This method was used to provide more stable outcomes, but it did not affect cost-effectiveness results because the results are presented as the difference between the different treatment options. Patients were enrolled over a period of 10 y, which implied that, overall, 4,800 patients were enrolled.

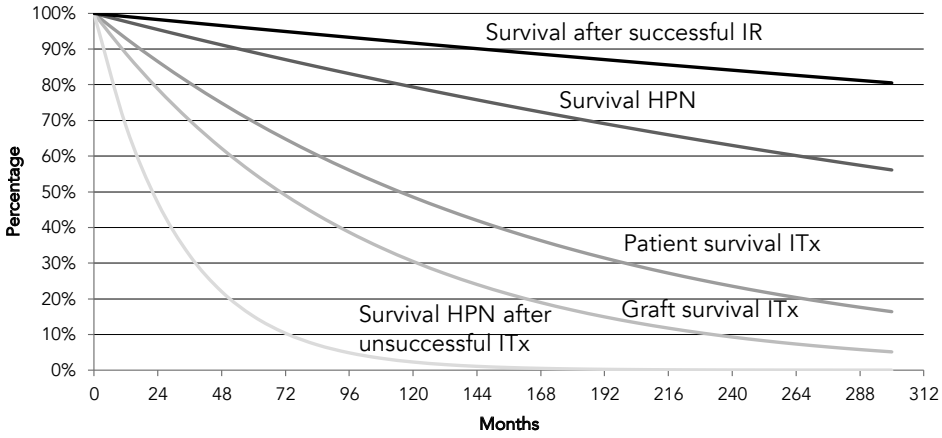
For our model, we assumed that 60-70% of the children had SBS, 10-20% had motility disorders, and 10-20% of the children had an enteropathy in agreement with previous reports from the literature.[7,18] Selections for IR and ITx were determined by fixed percentages of patients suitable for IR (67%) or ITx (10%). Children were eligible for ITx if their expected remaining survival time while receiving HPN was 12 mo. Survival while receiving HPN was based on data from the literature[6] and our own data. Graft and patient survivals after ITx were based on Intestinal Transplant Registry data. Survival data

Table 1. Model variables and parameters for IF in children[1]

Variable	Value	Source
Annual inflow of IF patients, *n*	480	NA
Proportion indication for IR, %	67	DRIFT
		Dutch HPN centers
		[7,18,19]
Duration of IR, d	279 (12-503)	HPN centers
Mortality during IR, %	2.6 – 11	HPN centers
		[20]
Proportion successful IR, %	80	HPN centers
		[20]
		[21]
Proportion indication for ITx, %	10	DRIFT
		Expert opinion

Abbreviations: [1] DRIFT, Dutch Registry of Intestinal Failure and Intestinal Transplantation; HPN, home parenteral nutrition; IF, intestinal failure; IR, intestinal rehabilitation; ITx, intestinal transplantation; NA, not applicable.

Figure 2. Survival curves applied in the simulation model for patient survival after successful IR (survival after successful IR), patient survival with HPN, patient survival after ITx, graft survival after ITx, and survival with receipt of HPN after an unsuccessful ITx (graft failure)



Abbreviations: HPN, home parenteral nutrition; IR, intestinal rehabilitation; ITx, intestinal transplantation.

were extrapolated to 40 y (**Figure 2**). The probability of dying while waiting for ITx was considered negligible.

Costs

We set out to calculate the treatment costs of patients who received IR and of patients who were receiving HPN but were not offered IR (**Table 2**). To this aim, we used data of

Table 2. Costs of pediatric IF treatment[1]

Treatment	Average cost
IR, €	
First year, total	265,132
Hospital admissions	206,759
Interventions	10,304
Diagnostics	1787
Outpatient visits	766
HPN administration	51,028
Dieticians' consults	980
Subsequent annual costs, total	30,262
Autonomy, €	
First year, total	8085
Subsequent annual costs, total	658
HPN, €	
First year, total	233,715
Hospital admissions	171,444
Interventions	5971
Diagnostics	1580
Outpatient visits	908
HPN administration	46,371
Dieticians' consults	1295
Subsequent annual costs, total	45,890
ITx, €	
First year, total	217,593
Transplant surgery	11,852
Other interventions	19,904
Blood products	621
Hospital admissions	167,718
Interventions/Diagnostics	855
PN	6742
Outpatient visits	3848
Medication	7592
Subsequent annual costs, total	42,443

Legend: [1]All data were derived from the HPN centers, with the exception of the costs of ITx, which were based on data from the ITx center.
Abbreviations: HPN, home parenteral nutrition; IF, intestinal failure; IR, intestinal rehabilitation; ITx, intestinal transplantation; PN, parenteral nutrition.

31 children who received IR (29 children with SBS and 2 children with an enteropathy, all of whom were able to wean off PN) and of 10 children who were receiving HPN (all of whom were suffering from motility disorders or enteropathies and were not able to wean off PN) and were attending the IF outpatient clinic at the Erasmus MC - Sophia Children's hospital between August 2003 and January 2014 (median PN duration: 583 d).

Children who received IR in our center frequently visited the outpatient clinic (every 2-12 wk depending on the age and condition of the patient). Their nutritional intakes and growths were evaluated, and laboratory values were monitored. Radiology and surgery (including intestinal-lengthening procedures) were performed when necessary. The nutrition (both PN and enteral nutrition) was adjusted, and medication (such as antibiotics or cholestyramine) was given when indicated. Children who were receiving HPN but were not eligible for IR also visited our outpatient clinic regularly (every 4-12 wk depending on the age and condition of the patient). Their growth and laboratory values were monitored, and PN was adjusted when necessary. Both children who were receiving IR and children who were receiving HPN were seen by the multidisciplinary team, which consisted of pediatric surgeons, pediatric gastroenterologist, dietitians, specialized nurses, and pharmacists.

For both groups, we retrospectively obtained data from the onset of IF regarding hospital days (either intensive care unit, high-care unit, general ward or daycare), surgical interventions (including intestinal-lengthening procedures in the IR group), diagnostic radiology, outpatient visits to the multidisciplinary IF team, dietary consultations (either inpatient or outpatient), and PN. Costs of intestinal autonomy (i.e., costs in the period after weaning off PN after successful IR) were calculated separately on the basis of the same variables. Data regarding ITx, including hospitalization, ITx procedure with blood products, other surgical interventions, radiology, visits to the ITx team, dietary consultations, PN, and immunosuppressive medication, were obtained for 5 children (with enteropathy (n=3), SBS (n=1), and motility disorder (n=1)) who underwent ITx in the Netherlands.

After this data collection, costs were calculated by multiplying the volumes of healthcare use with the corresponding cost prices. According to guidelines for costing studies in healthcare[22], we calculated integral cost prices for the variables. Because tariffs are not accurate measures of costs, we set out to calculate real economic costs. Costs of hospital days, surgical interventions, visits to the IF team, and dietary consultations were largely based on cost prices of the hospital. All costs compromised both personnel costs (including costs of medical specialists) and nonpersonnel costs (including materials, equipment, and overhead costs such as housing, utilities, cleaning, management). Personnel costs were based on the Collective Agreement for University Medical Centers. Cost prices of diagnostic radiology were based on national tariffs determined by the Dutch Healthcare Authority, which included both an amount to cover the hospital costs and an amount to

cover the services of the medical specialist. Costs of PN were calculated with the use of mean intakes that were obtained from the hospital records every 3 mo. The cost price of PN was based on the delivery rates in 2014 in our hospital and also included personnel costs, disposables, equipment, overhead, and transportation to the patient. Costs of immunosuppressive medication were calculated with the use of the pharmacists' purchase prices.

All costs were reported in euros (€) and were calculated for the year 2014 (with a few exceptions, which referred to the year 2012, because more recent cost prices were not available at the time). Costs were divided into the first year after start of IF and follow-up y. With consideration of the fact that the last year often did not constitute a full year, we adjusted for this variance and used corrected costs in the simulation model.

Cost-effectiveness

During the execution of the model, detailed information was collected about the time spent in the various treatment states. To estimate life-years for the scenarios with and without IR, we added up the number of patients in the different states (IR, intestinal autonomy, HPN, and ITx) per year. We evaluated the cost-effectiveness of IR by comparing life-years and costs of 500 replications of the model with and without IR as a treatment option. To calculate the incremental cost-effectiveness ratio (ICER), which was defined as the difference in costs divided by the difference in life-years, we combined life-years and number of patients with costs for the scenario with IR and for the scenario without IR. The ICER expresses the costs for the gain of a life-years. Costs and effects (i.e., life-years) that were to occur in the future were discounted to their current values.[23] This calculation was done to reflect the fact that individuals prefer current benefits over those in the future and prefer future costs over current costs. We discounted future costs by 4.0% and effects by 1.5% according to the Dutch guidelines for costing studies in healthcare.

Sensitivity analysis

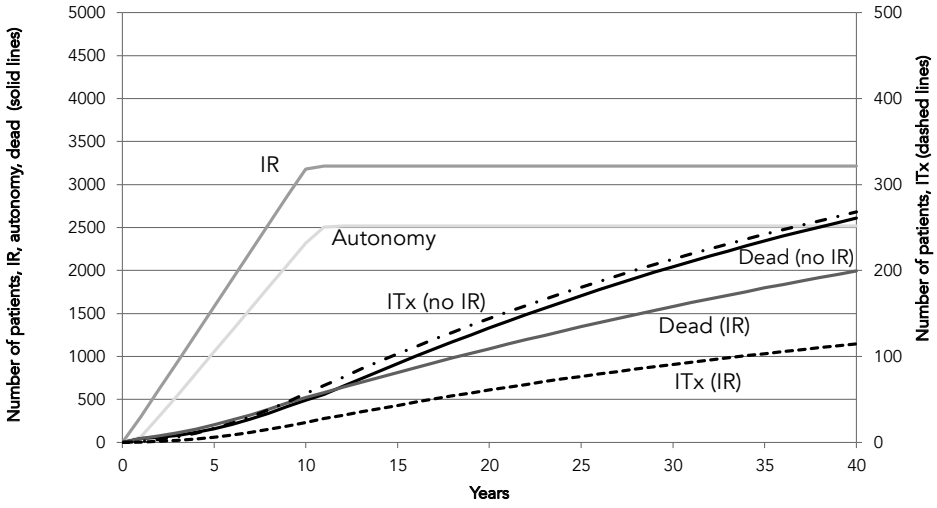
In addition to the base case scenario, we performed sensitivity analyses with a variable percentage of successful IR (60% rather than 80%), a variable percentage of indication for ITx (20% rather than 10%), the expected survival of patients who were receiving HPN to be eligible for ITx (18 mo rather than 12 mo), and variations of cost estimates (costs of IR and autonomy increased by 25%, and costs of HPN and ITx decreased by 25%).

RESULTS

Effectiveness

The number of patients who were treated with IR and, therefore, also the number of patients who achieved intestinal autonomy, increased during the 10 y in which patients were enrolled (**Figure 3**). These numbers were stable shortly after the end of the enrollment period because of the short median time of IR (279 d). The number of patients who were receiving PN were the same in the scenario with IR and the scenario without IR because all patients received a few days PN before they were assigned to either HPN or IR treatment. The number of patients who were receiving HPN declined steadily after the enrollment period because of ITx or death (**Figure 4**). At the end of the simulation period of 40 y, there were 933 patients left in the HPN group (19% of enrolled patients) in the scenario with IR and 2161 patients left (45% of enrolled patients) in the scenario without IR (Figure 4). In the scenario with IR, 1860 patients achieved intestinal autonomy (58% of the number of patients who were undergoing IR) (Figure 3). A total of 115 patients underwent ITx in the scenario with IR compared with 268 patients in the scenario without IR (Figure 3). The mean number of deceased patients was 1995 individuals (42% of the total enrolled) in the scenario with IR and 2610 individuals (54% of the total enrolled) in

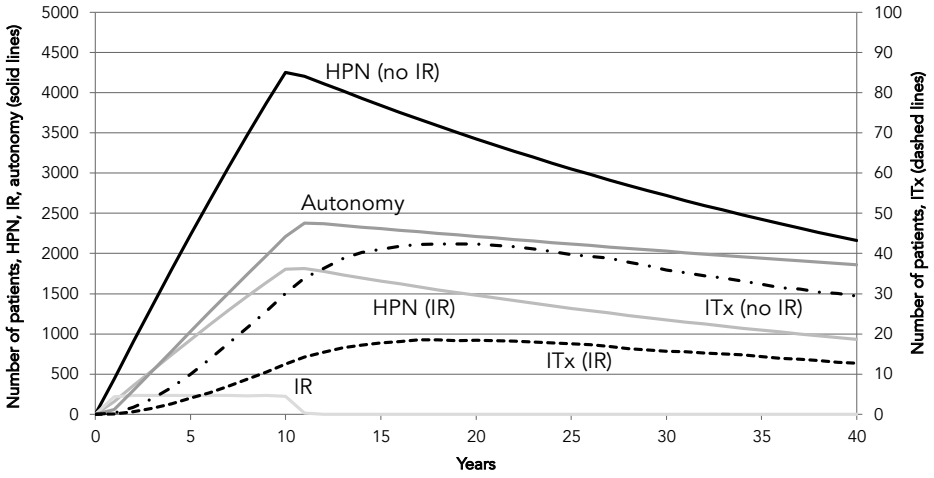
Figure 3. Cumulative number of patients over time in various states in the simulation model



Legend: HPN and IR are plotted on the left y-axis. ITx is plotted on the right y-axis. The 2 uppermost gray lines represent the cumulative numbers of patients undergoing IR and the cumulative numbers of patients who achieved intestinal autonomy, respectively. Dashed lines represent the cumulative number of patients who were undergoing ITx in the scenario without IR (dashed-dotted line) and in the scenario with IR (dashed line), both of which are plotted on the right y axis. The black line represents the cumulative number of deceased patients when the scenario without IR was applied. The lowest grey line represents the cumulative number of deceased patients in the scenario with IR.

Abbreviations: HPN, home parenteral nutrition; IR, intestinal rehabilitation; ITx, intestinal transplantation.

Figure 4. Distribution of patients over time in various states in the simulation model



Legend: HPN and IR are plotted on the left y-axis. ITx is plotted on the right y-axis.
Abbreviations: HPN, home parenteral nutrition; IR, intestinal rehabilitation; ITx, intestinal transplantation.

the scenario without IR (Figure 3). In addition, the mean number of life-years per patient was 19.4 in the scenario with IR and 18.2 in the scenario without IR (discounted).

Costs

The total first-year cost of IR was €265,132, whereas the cost in subsequent years was estimated at €30,262/y (**Table 2**). Costs mainly compromised hospital admissions (80% for the first year and 57% for subsequent years) and PN administration (19% for the first year and 39% for subsequent years). When patients achieved intestinal autonomy, costs were €8,085 in the first year and, on average, €658/y in the subsequent years. The cost of HPN was €233,715 in the first year, which mainly arose from hospital admissions and PN administration. Costs of hospital admissions were higher for patients who were receiving IR than for patients in the HPN group. The cost of ITx in the first year was €217,593, which was also mainly composed of hospital admissions. Average total costs (discounted) per patient were €819,292 in the scenario with IR compared with €1,176,830 without IR.

Cost-effectiveness

Compared with the scenario without IR, the scenario with IR resulted in an overall increase of 9690 life-years (**Table 3**, undiscounted). The mean number of life-years per patient was 19.4 in the scenario with IR compared with 18.2 in the scenario without IR. The scenario with IR resulted in total cost savings of greater than €4 billion. This amount resulted in cost savings of €435,000 for each additional life-year gained by IR. When we applied discounting, the ICER per life-year gained was €280,600.

Table 3. Effects and costs of treatment of children with IF with and without IR[1]

Outcome	With IR (IR + HPN + ITx)	Without IR (HPN + ITx)	Difference IR vs. no IR
Patients, n			
IR	3215	0	
HPN	4800	4800	
ITx	115	268	
Life-years (undiscounted)			
IR with subsequent autonomy	76,319	0	
HPN	49,478	115,406	
ITx	534	1235	
Total	126,331	116,641	9690
Mean life-years per patient, years (undiscounted)	26.32	24.30	2.02
Costs (undiscounted), €			
IR with subsequent autonomy	1,145,631,157	0	
HPN	5,278,540,318	10,584,334,490	
ITx	78,847,425	148,774,459	
Total	6,517,939,258	10,733,108,949	4,215,169,691
Average total costs per patient (undiscounted), €	1,357,904	2,236,064	878,160
Life-years (discounted at 1.5%)			
IR with subsequent autonomy	55,994	0	
HPN	36,946	86,319	
ITx	382	887	
Total	93,322	87,206	6116
Mean life-years per patient, years (discounted at 1.5%)	19.44	18.17	1.27
Costs (discounted at 4%), €			
IR with subsequent autonomy	906,814,494	0	
HPN	2,938,481,774	5,579,390,683	
ITx	42,306,644	69,394,567	
Total	3,932,602,912	5,648,785,250	1,716,182,338
Average total costs per patient (discounted at 4%), €	819,292	1,176,830	357,538

Legend: [1]Mean patient numbers and life-years and average total costs of all patients are shown.
Abbreviations: HPN, home parenteral nutrition; IF, intestinal failure; IR, intestinal rehabilitation; ITx, intestinal transplantation.

Sensitivity analysis

Because the percentage of success of IR can differ in centers and countries, an analysis with a percentage of success of 60% was also performed. As expected, total life-years were lower and total costs were higher, than with a percentage of success of 80% (**Table 4**). This analysis resulted in estimated costs savings of €499,752 for each additional life-year gained by IR. When discounting was applied, this amount decreased to €308,073.

Table 4. Sensitivity analysis of the percentage of success of IR, indication for ITx, and expected survival of patients who were receiving HPN to be eligible for ITx[1]

Outcome	With IR (IR + HPN + ITx) Successful IR = 60%	With IR (IR + HPN + ITx) Indication ITx = 20%, expected survival on HPN 18 mo	With IR (IR + HPN + ITx) Indication ITx = 10%, expected survival on HPN 18 m
Undiscounted			
Life-years	122,357	126,985	126,295
Costs, €	7,876,761,479	6,621,022,818	6,516,486,576
Difference vs. no IR			
Life-years	5716	8775	9768
Costs, €	-2,856,347,470	-4,289,133,613	-4,208,000,731
Discounted			
Life-years	90,676	93,803	93,306
Costs, €	4,579,636,971	3,981,877,095	3,933,994,328
Difference vs. no IR			
Life-years	3470	5443	6162
Costs, €	-1,069,148,279	- 1,754,249,084	-1,714,533,344

Abbreviations: HPN, home parenteral nutrition; IF, intestinal failure; IR, intestinal rehabilitation; ITx, intestinal transplantation.

When we selected a higher percentage of patients for ITx (20% instead of 10%), the total amount of life-years slightly increased, and the total costs slightly decreased. The result was that the costs per life-year gained (both undiscounted and discounted) basically remained unchanged. When we increased the expected survival of patients who were receiving HPN to be eligible for ITx to 18 mo, the results were comparable with the basic situation of our model.

Variations in costs of IR, autonomy, HPN, and ITx had a modest effect on the cost-effectiveness. With consideration of a worst-case scenario of increased costs of IR and autonomy by 25% and decreased costs of HPN and ITx by 50%, IR was still cost-effective with estimated costs savings of €148,603/life-year gained (discounted).

DISCUSSION

This study yielded insight into the costs of pediatric IF and the cost-effectiveness of IR. The study revealed that the annual costs of pediatric IF are very high ranging from €234,000 to €265,000 for the first year and €46,000 to €30,000 for subsequent years. According to our simulations, IR prolonged the average patient survival by 1.2 y over a 40-y period. The cost savings that were achieved per life-year were estimated at €280,600. Because our simulation showed that IR improves patient survival while saving costs, we consider IR to be a cost-effective treatment of children with IF. These results are relevant to both the medical community and health authorities, who, in different roles, have a joint responsibility for the efficient spending of scarce resources, which has become a top priority in today's healthcare systems.

To our knowledge, this is the first study to have evaluated the cost-effectiveness of IR. In general, studies on costs of pediatric IF have been scarce. However, there have been a few studies on the costs of pediatric SBS, which is the main cause of IF in children. A previous study from our center reported that the average total cost for children with SBS was €269,700.[10] The cost, which included costs that were related to first admission and follow-up, was for follow-up that varied between 9 mo and 5.5 y (median: 1.5 y). This average total cost is comparable with our current results as was the distribution of these costs (see Table 2). In our study, the bulk of costs were related to hospital admissions, especially the first admission which included the start of IF. Children with IF are frequently admitted to the hospital and often for a prolonged period. In addition, PN for children is mostly customized and, therefore, more expensive than PN for adults. Costs of hospital admissions were higher for patients receiving IR than for patients in the HPN group, especially in the first year. This difference might be explained by the fact that children who were receiving IR were mostly patients with SBS who often needed several operations. These factors may have consequently led to longer hospitalizations and higher costs. More recently, Longworth et al.[13] showed that the average costs of stable SBS patients (N=24) was £159,000/patient over 30 mo based on 1998 and 1999 prices, which was equivalent to ~ €190,000 in 2014. The lower costs in their study might be explained by the fact that the median PN duration before inclusion was 9 mo, and these data before inclusion in the study were not included in the calculation of the costs. A study in the United States[11] reported an average total cost of 1.6 million US$ over a 5-y period for children with SBS. However, this calculation was based on billable charges and not on actual costs, which made a comparison with our study difficult.

In addition to the studies that have evaluated the costs of pediatric SBS, some studies have been performed on the costs of ITx. Abu-Elmagd et al.[12] reported an average cost of 132,285 US$ for an isolated intestinal transplant. Another study reported an average

cost of an isolated intestine of 135,000 US$.[9] However, these costs were based on the US situation and on an average of adults and children and did not provide details as to the allocation of costs. A British study in children reported average treatment costs of transplanted children of £275,000 (equivalent to ~ €329,000 in 2014) over 30 mo[13], which is quite comparable to our results.

To make our study generalizable to other countries, we precisely described the variables and costs that we used for our model. The changing of these variables to figures that are relevant to another country can give an impression of the outcomes for other countries. However, it still remains difficult to compare costs between different countries because of differences in prices and differences in how the care for children with IF is organized and charged.

When looking at the cost-effectiveness, IR improved the average patient survival by 1.2 y over a 40-y follow-up period. This increase in patient survival may seem marginal and might be due to the fact that IR is not successful for all children who are eligible for IR. Some children will not gain extra life-years, whereas other children will gain > 1.2 life-years. Survival in this study was based on the literature[6] and was extrapolated to 40 y. As a result, we may have underestimated the survival of children with IF because recent publications have shown survival rates of 84%[24] and 90%[7] after 15 and 14 y, respectively. The survival data from these publications were based on both children who were receiving HPN and were not able to wean off PN and children who were undergoing IR. When these data would be applied to our model, survival would improve in both HPN and IR groups, and thus, we expect that the cost-effectiveness of IR will not change. In addition, it is not certain whether these survival rates will apply for 40 y.

The number of children who were undergoing ITx may have influenced the costs of ITx and, therefore, also the outcomes of our model. At the same time, indication rates may differ in countries. On the basis of the strict application of indications in the Netherlands, we assumed that 10% of the children met the indications for ITx. When we evaluated the cost-effectiveness of IR with the assumption of an ITx-indication rate of 20%, the costs per life-year gained remained basically unchanged. Another factor that may have an influence on the number of children who are undergoing ITx is the estimated prognosis for HPN that is necessary to be eligible for ITx. In our model, we used an expected survival of patients who were receiving HPN of 12 mo before patients could have undergone ITx. The increase of the expected survival of patients who were receiving HPN from 12 to 18 mo did not change the outcomes. Lastly, we performed a worst-case scenario analysis with increased costs of IR and autonomy, and decreased costs of HPN and ITx. Despite these changes, IR was still cost-effective. These findings suggest that IR is not only cost-effective in the Netherlands but may also be cost-effective in other countries or

settings where higher numbers of patients for an ITx are common and where costs may be different.

There are 4 points to consider when interpreting the results of our model. First, costs of IR and HPN were based on only 41 children, and costs of ITx were based on 5 children after ITx. Although small, we believe that our patient population of 41 children reflects the whole spectrum of children with IF in the Netherlands. Because ITx has been performed in only 5 children in the Netherlands, it was not possible to calculate costs for more children after ITx. In addition, the costs in subsequent years, which covered the 40-y time horizon of the model, had to be estimated on the basis of a relatively short follow-up period. Second, we calculated only direct and indirect costs inside the healthcare sector. We did not include indirect costs outside the healthcare sector, such as inability of parents to work, because this aspect fell outside the scope of the current study. We also excluded costs of laboratory tests, intercollegial consultations, and medications (other than immunosuppressive medication); however, these costs made up only a minor proportion of the total costs. Further, we did not calculate costs of the enteral nutrition because these costs were also a minor proportion of the total costs, and it is likely that these costs do not differ much in the different treatment options. Third, our model did not include outcome measures such as QoL , growth, and the number of complications. The inclusion of QoL, would have made it possible to calculate quality-adjusted life-years, which are a more generic outcome measure used in cost-utility analysis, but the evidence on QoL in children with IF has been both scarce and ambiguous. Growth was not included in the model because the aim of optimal growth (i.e., maintaining growth within a target height range) was the same for all groups (IR, HPN, and ITx). Complications were only indirectly included in the model when they led to costs (e.g., because of hospital admission or surger) or death. Fourth, although information that was used for the model was obtained from the literature or from actual data in our own population, some assumptions were necessary. Therefore, we performed sensitivity analyses to test the robustness of the results to certain assumptions that were made, and we were transparent about the decisions that were made regarding the methods of the study.

In conclusion, our model shows that IR improves the survival of children with IF and is associated with cost savings. Therefore, we consider IR a cost-effective treatment of children with IF. In the future, this model could also be used to evaluate the cost-effectiveness of ITx in children with IF.

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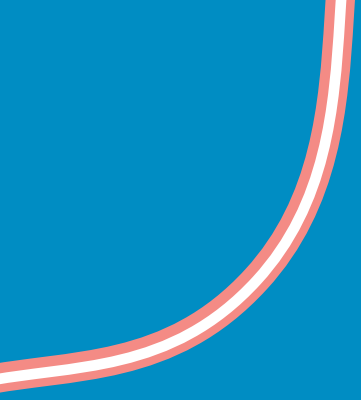

11

Wide variation in organisation and clinical practice of paediatric intestinal failure teams: an international survey

Clin Nutr. 2018 Dec;37(6 Pt A):2271-2279.

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ABSTRACT

Background & aims

We aimed to assess the current organisation and clinical practice of teams treating children with intestinal failure (IF) across Europe and compare the results with the current guideline.

Methods

A two-part online survey was sent to all the major European specialist IF services. The first part concerned general information about the team and patients monitored. The second part concerned important care topics such as vascular access and monitoring of complications. No patient identifiers were collected.

Results

Seventy-three respondents completed the first part, representing 61 teams in 20 countries. The median number of children on parenteral nutrition (PN) at home per team was 15 (range 1–125). Teams consisted of the following members: paediatric gastroenterologist (present in 100% of the teams), dietitian (95%), specialist nurse (92%), paediatric surgeon (89%), pharmacist (82%), psychologist (66%), social worker (62%), speech therapist (48%), physiotherapist (38%), general paediatrician (33%). The second part was completed by 67/73 respondents (59/61 teams). Vascular access care was comparable with the guideline. Somatostatin analogues were prescribed by 14% of the IF teams and probiotics by 44% of the teams. Prophylactic anticoagulation was used by 46% of the teams. In 81% of the teams a multicomponent lipid emulsion containing fish oil was routinely used. Bone densitometry was regularly performed in 75% of teams, but never performed in 19%.

Conclusions

In conclusion, there is a wide diversity of composition of IF teams and their number of patients treated. Overall, there is good compliance to the current guideline. Clinical practice that varied most was the standard use of medication such as probiotics and somatostatin analogues, and standard monitoring of long-term complications. Experience regarding specific treatment options should be shared. Moreover, international agreement on standards of care with focus on implementation of the guideline is needed to optimise care and improve outcomes of children with IF.

INTRODUCTION

Children with intestinal failure (IF) depend on parenteral nutrition (PN). When IF is irreversible for several months, PN can be given at home as home PN (HPN). Despite the complexity of the treatment, there is a scarcity of available evidence-based guidelines for the treatment of these patients. The guideline that is currently mostly used in Europe is provided by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN).[1] This is a guideline on paediatric PN, including chapters on HPN and complications of PN. Due to the lack of good quality trials in children with IF, many of the recommendations provided by this guideline are based on limited evidence and largely driven by expert opinion. Additionally, this guideline was based on literature published before 2004 and clinical practice may have changed since then.

One of the recommendations of this guideline is that the management of children with HPN should be undertaken by multidisciplinary teams, including physicians, pharmacists, nurses, dietitians, social workers and psychologists.[1] There are, however, no data available about the organisation of existing paediatric IF teams and current clinical practices are unknown. The purpose of our study was therefore to provide an overview of the organisation and current practice of specialised paediatric IF teams across Europe and compare these results to the ESPGHAN/ESPEN guideline.[1] With this knowledge, future harmonisation and optimisation of clinical guidelines could be achieved. Our hypothesis was that the current guideline has not been universally implemented, leading to a wide variation in clinical practice. We expected that differences are the most striking in areas with the weakest evidence. To assess the differences and similarities, we performed a survey among European paediatric IF teams.

MATERIAL AND METHODS

We conducted a two-part online survey between September 2016 and January 2017. The online survey consisted of 40 questions regarding local protocols and strategies and was provided in English. The questionnaire is available as supplement (Supplementary data 1). Testing of clarity and relevance of the survey was performed by four independent clinicians in four centres (Erasmus Medical Center-Sophia Children's Hospital, Rotterdam, the Netherlands; Academic Medical Center-Emma Children's Hospital, Amsterdam, the Netherlands; University Hospital of Gent, Belgium; and Great Ormond Street Hospital, London, United Kingdom).

In the first part of the survey, respondents were asked to fill in some general information about their IF team and the number of patients monitored by their team. Respondents who completed the first part of the survey were invited for the second part. This part concerned specific topics important in the care of children with IF on HPN. Several reminders via e-mail were sent after the first invitation. If more than one questionnaire was returned from a single IF team, the mean of the received answers was used.

Since there is no overall list available of centres providing HPN in Europe, an invitation to the survey was electronically sent to members of the ESPGHAN Network for IF and Transplantation, to members of the British Society of Paediatric Gastroenterology, Hepatology and Nutrition (BSPGHAN) and to members of the special interest group Paediatrics of ESPEN (not necessarily known to have an IF team). In addition, respondents were asked to forward the survey to other IF teams in their country or members or colleagues involved in the management of children with IF. Therefore, it is not known exactly how many IF teams were invited to complete the survey.

The local Institutional Review Board of the Erasmus MC in Rotterdam waived the need for informed consent (MEC-2016-503) since no patient identifiers were collected. The trial was registered in the Dutch Trial Register at number 6062 (http://www.trialregister.nl).

Statistical analysis was performed using IBM SPSS statistics 21 for Windows (IBM, Armonk, New York). Categorical variables were summarised as frequencies and percentages, and continuous variables as mean ± SD when normally distributed or as median and interquartile range (IQR) or range when not normally distributed. Data obtained from the survey were compared to the current ESPGHAN/ESPEN guideline.[1] Differences between teams with ≤ 10 patients on HPN and teams with >10 patients on HPN were analysed using the Chi-square test. Statistical significance was defined as a p-value <0.05.

RESULTS

Part one: general information of IF teams

Seventy-four respondents completed the first part of the survey. One was a duplicate reply and therefore deleted. None of the other questionnaires were removed because of missing data. Seventy-three questionnaires were analysed, representing 61 teams in 20 countries, as shown in **Figure 1**.

Figure 1. Sixty-one teams (in yellow) from 20 countries (in blue) participated in the survey. Israel is not shown on map.

In 9 centres, more than one member of the IF team completed the first part of the questionnaire with a maximum of 3 completed questionnaires in one centre. The questionnaire was filled in by different members of the IF teams, distributed as follows: 58 paediatric

gastroenterologists, 4 dietitians/nutritionists, 3 paediatric surgeons, 3 paediatricians, 3 nurses/nurse practitioners, 1 paediatric hepatologist and 1 paediatric metabolic diseases specialist. Ninety percent of the teams were linked to university hospitals and 9 of the teams (15%) were combined with an adult IF team. All IF team characteristics are shown in **Table 1**. Regarding the composition of the IF team, 46% of the teams consisted of a physician, pharmacist, nurse, dietitian, social worker and psychologist. Other IF teams members mentioned besides the ones shown in Table 1, were transplant surgeon, occupational therapist, endoscopist, home team nurses, interventional radiologist, microbiologist and a nutrition physiologist.

Part two: specific topics important in the care of children with IF

In total, 67 respondents (92%) also completed the second part of the survey, representing 59 of the 61 IF teams (97%) completing the first part.

Vascular access

According to the survey, most IF teams (97%) used tunneled central venous catheters (CVC) (for example Broviac® or Hickmann®) as their first choice. A port-a-cath was (also) standardly used by 10% of the teams, followed by a peripherally inserted central catheter (PICC) in 7% of the teams.

Catheter lock solutions were used by 90% of the teams; in 42% of the teams taurolock™ (combination of taurolidine and citrate) was standardly used, and in 22% and 15% of the teams heparin lock and taurosept® (containing taurolidine) were used respectively (multiple answers per team possible).

Forty-six percent of the teams used anticoagulation as primary prophylaxis in the prevention of catheter-related thrombosis or occlusion. LMWH was the standard in 14% of the teams, whereas heparin lock and vitamin K antagonists were standardly used in 12% and 2% (multiple answers per team possible). LMWH was sometimes used in 19%, followed by heparin lock and vitamin K antagonists in 17% and 14% of the teams (multiple answers per team possible). Reasons for not giving anticoagulation were no evidence (17%), not necessary/no thrombosis seen (7%) and potential side effects (3%). Other reasons mentioned not to give anticoagulation were to decrease the number of manipulations of the CVC and to avoid incompatibility. Additionally, in 19% of the teams anticoagulation was given only when there was a coagulation disorder/hypercoagulable state, for example if there were genetic hyper-coagulation factors present, or other risk factors (previous thrombosis, infection episodes), or when acute thrombosis was suspected or diagnosed.

Table 1. Characteristics of the IF teams (number of teams = 61)

Characteristic			
Experience of IF team	**% of teams**		
<1 year	2		
1 – 5 years	5		
6 – 10 years	15		
11 – 20 years	49		
>20 years	30		
Types of specialists represented in IF teams	**% of teams**	**Number: median (min-max)**	**Hours per week working for IF team per health care professional (median, (IQR)**
Paediatric gastroenterologist	100	2 (1-6)	5 (2-10)
Dietitian	95	1 (0-4)	5 (2-11)
Specialist nurse	92	1 (0-8)	10 (3-20)
Paediatric surgeon	89	2 (0-5)	1 (1–2)
Pharmacist	82	1 (0-3)	5 (2-15)
Psychologist	66	1 (0-2)	2 (1-5)
Social worker	62	1 (0-2)	2 (1-5)
Speech therapist	48	0 (0-2)	2 (1-5)
Physiotherapist	38	0 (0-3)	3 (1-8)
General paediatrician	33	0 (0-5)	5 (2-14)
Number of children on HPN per team	**Median (IQR, min-max)**		
Total	15 (7-21, 1-125)		
Infants (1 month – 1 year)	1 (1-3, 0-25)		
Children (1 – 5 years)	5 (2-9, 0-45)		
Children (5 – 10 years)	3 (2-5, 0-34)		
Children (10 – 15 years)	2 (1-5, 0-30)		
Adolescents (>15 years)	1 (0-2, 0-15)		
Underlying diseases of children on HPN per team	Median (IQR, min-max)		
Short bowel syndrome (SBS)	8 (4-12, 0-88)		
Motility disorder	3 (2-7, 0-29)		
Enteropathy	2 (0-5, 0-23)		
Monitoring of children weaned off HPN	93% of teams		
Number of children weaned off PN monitored by the IF team	Median (IQR, min-max) 11 (6-20, 1-114)		

Abbreviations: HPN, home parenteral nutrition; IF, intestinal failure; IQR, interquartile range; SBS, short bowel syndrome.

Parenteral nutrition

HPN was provided pharmacy-customised and age-weight specific in 78% of the IF teams, as commercial mixed bags in 25% of teams and as commercial mixed bags customised by the pharmacy in 31% of teams (multiple answers per team possible). The type of lipid emulsions used are shown in **Table 2** and an overview of the lipid targets used for infants and older children by the IF teams are shown in **Figure 2**.

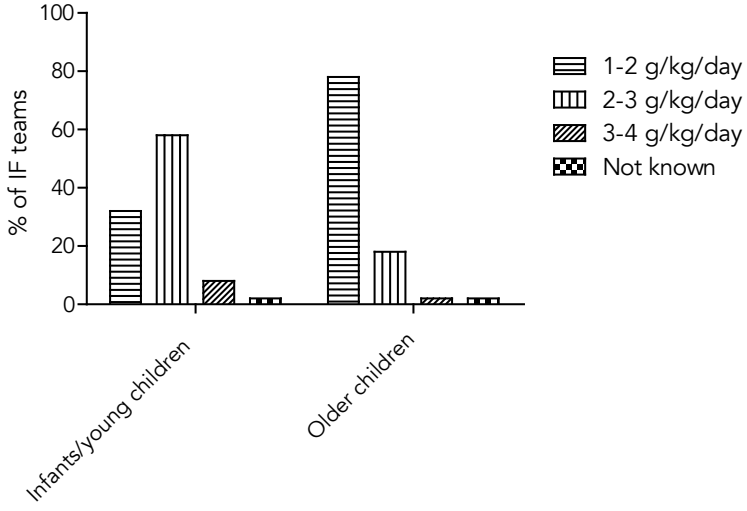
Concerning the maximum amount of parenteral carbohydrates used, 92% of teams reported 16-20 g/kg/d. The protein target as described by the ESPGHAN/ESPEN guideline was followed by 97% of the teams. One team used 2.5-3 g/kg in infants <2 year,

Table 2. Parenteral lipid emulsions used for HPN

Lipid emulsions	Number of IF teams n (%)		
	Standard	**Sometimes**	**Never**
100% soybean based (for example Intralipid®)	4 (7)	12 (20)	43 (73)
Soybean/MCT/olive/fish oil (for example SMOFlipid®)	48 (81)	10 (17)	1 (2)
100% Fish-oil (for example Omegaven®)	3 (5)	33 (56)	23 (39)
Olive/soybean (for example Clinoleic®)	15 (25)	16 (27)	28 (48)
Soybean/MCT (for example Lipoplus®)	4 (7)	4 (7)	51 (86)

Abbreviations: HPN, home parenteral nutrition; IF, intestinal failure; MCT, medium chain triglycerides.

Figure 2. Parenteral lipid targets in infants and older children in g/kg/day



Legend: Boxes represent the number of IF teams.
Abbreviation: IF, intestinal failure.

2-2.5 g/kg for children 2-10 years and 2 g/kg/d for children >10 years, and 1 team used the ratio between calories and nitrogen. In children on full PN, lipids were given 7 nights/week by 46% of the teams, in 5-6 nights by 34% of the teams, in less than 5 nights by 17% of the teams.

In 90% of the teams, HPN was administered by the parents. In other teams, it was administered by home care companies (9%) or hospital nurses in 1 team. In almost all teams, parents were trained by hospital nurses, sometimes continued at home by the companies that provide HPN or by home care companies. The duration of the training varied between 10 hours and 3 months, most of them between 1 and 4 weeks. The HPN was funded by government and/or hospital in 48% of the teams, by health insurance in 39% of the teams, or a combination (2%). In one team, the HPN was paid by the parents.

Enteral/oral nutrition

When oral or enteral nutrition (EN) was started in neonates/infants, breast milk was recommended by 88 % of the teams (**Table 3**). In older children, solid oral feeding was mostly used.

EN was given as a combination of intermittent and continuous feeding (for example 20 h tube feeding with 2 bolus/bottle feeds during the day) by 44% of the IF teams. Some of the teams mentioned that they start with bolus feeds and try continuous feeds overnight combined with bolus feeding during the day when reaching the limit of increasing the EN, whereas other teams mentioned that they start with continuous feeding and later start oral bolus feeding.

In 70% of the IF teams, a speech therapist was involved in the introduction of oral feeding.

Table 3. Use of different types of nutrition in neonates/infants and older children

Number of IF teams n (%)	Standard	Sometimes	Never	Unknown
Neonates/infants				
Breast milk	52 (88)	6 (10)	1 (2)	-
Polymeric formula	9 (15)	42 (71)	7 (12)	1 (2)
Oligomeric formula	13 (22)	44 (75)	2 (3)	-
Monomeric formula	7 (12)	45 (76)	4 (7)	3 (5)
Older children				
Polymeric formula	30 (51)	27 (46)	2 (3)	
Oligomeric formula	15 (25)	39 (66)	4 (7)	1 (2)
Monomeric formula	5 (9)	43 (73)	10 (17)	1 (2)
Solid oral feeding	33 (56)	22 (37)	3 (5)	1 (2)

Abbreviation: IF, intestinal failure.

Nutritional status/bone health/micronutrients

For standard monitoring of growth and nutritional status, weight (100%), height (98%), blood parameters (92%) and head circumference (81%) were used most frequently. Two of the teams mentioned that also bio-electrical impedance analysis was used, and 2 of the teams also monitor body composition and perform indirect calorimetry. **Supplementary Table 1** shows the frequency of micronutrient monitoring. 25-OH vitamin D was measured by all teams (54% every 3 months), whereas vitamin B1, B2, B6 and active vitamin B12 were measured by 45-60% of the teams. In addition, manganese, aluminium and chromium were measured in 32-56% of the teams.

Bone health was monitored with blood parameters in all teams (in 95% every 6 months), whereas DEXA scans were performed regularly in 75% of teams (yearly in 32%) (**Supplementary Table 2**).

Psychomotor development

According to 64% of the IF teams, most of the children go to regular schools. In 31% of the teams, most of the children go to regular schools but with extra assistance. Only in 5% of the IF teams, most of the children go to special needs schools due to medical or intellectual reasons.

In 49% of the IF teams, neuropsychological and psychomotor development is standardly assessed.

Surgery

Serial transverse enteroplasty (STEP) procedures can be performed by 71% of the teams (with a maximum of 15 procedures per centre/year) and Bianchi procedures by 42% of the teams (with a maximum of 25 procedures per centre/year). In 20% of the IF teams, intestinal transplantation was performed with a maximum of 8 intestinal transplants in an individual centre per year.

Medication

Medication such as antibiotics as treatment for small intestinal bacterial overgrowth, antidiarrheal/antimotility agents and probiotics were regularly prescribed in 90%, 73% and 44% of the IF teams respectively (**Table 4**).

Comparison of smaller and larger centres and comparison with current guideline

We compared teams with ≤ 10 patients on HPN (41% of the teams) to teams with >10 patients on HPN (58%). Smaller centres were more often combined with adult teams (28% versus 6%, $p = 0.015$). Additionally, they significantly less often had a dietitian in the team (88% versus 100%, $p = 0.033$). There were no significant differences for

the other team members and no significant difference regarding the number of centres fulfilling the recommendation of the ESPGHAN/ESPEN guideline[1] for a multidisciplinary team between smaller and larger centres.

Table 4. Medication standardly used by IF teams (>1 answer possible per IF team)

Medication standardly used	Number of IF teams (%)
Antibiotics as treatment for small intestinal bacterial overgrowth (e.g. metronidazole)	53 (90)
Proton pomp inhibitor (e.g. omeprazole)	53 (90)
Antidiarrheal/antimotility agents (e.g. loperamide)	43 (73)
Bile acid sequestrant (e.g. cholestyramine)	38 (64)
Histamine receptor antagonist (e.g. ranitidine)	32 (54)
Probiotics	26 (44)
Prokinetic agents (e.g. erythromycin)	22 (37)
Somatostatin analogue (e.g. octreotide)	8 (14)
A2-adrenergic receptor agonist (e.g. clonidine)	2 (3)
Growth factors (e.g. Glucagon-like peptide-2 analogue teduglutide)	2 (3)

Abbreviation: IF, intestinal failure.

Prophylactic anticoagulation was used significantly more frequently in the teams with more patients (59% versus 28%, p = 0.019), as well as DEXA scans to monitor nutritional status (41% versus 16%, p = 0.038). Bianchi procedure was performed in 20% of the smaller centres compared to 59% of the larger centres (p = 0.003), whereas intestinal transplantation was performed in 8% of the smaller centres compared to 29% of the larger centres (p = 0.043). Regarding medication, proton pump inhibitors were more often used standardly in large centres (97% versus 80%, p = 0.032). For other standardly used medication there were no significant differences. Similarities and differences between the guideline and current practice according to our survey are shown in **Table 5**.

Table 5. Overview of recommendations by ESPGHAN/ESPEN and clinical practice based on the present survey

Element	ESPGHAN/ESPEN (2005) [1] - PN in infants, children and adolescents	Survey - practices of IF teams
Composition of IF team	Multidisciplinary team including physician(s), pharmacist(s), nurse(s), dietitian(s), social worker(s) and psychologist(s). (No GOR)	46% of the teams consisted of a physician, pharmacist, nurse, dietitian, social worker and psychologist.
PN - amino acids	Preterm infants: 1.5-4 g/kg/d (GOR A-B) Neonates: 1.5-3 g/kg/d (GOR D) 2 m – 3 y: 1.0-2.5 g/kg/d (GOR D-C) 3 – 18 y: 1.0-2.0 g/kg/d (GOR B-D)	Almost all teams follow guideline
PN - carbohydrates	Preterm infants: start with 4-8 mg/kg/min (GOR C), maximum 12 g/kg/d after birth (LOE 2-3) Term neonates/children - 2 y: maximum 18 g/kg/d (GOR C) Cyclical PN: maximal infusion rate 1.2 g/kg/hour (GOR C)	Varying glucose targets, mostly 16-18 g/kg/d, maximum of 20 g/kg/d
PN - lipids	Infants: maximum of 3-4 g/kg/d (GOR B) Older children: maximum of 2-3 g/kg/d (GOR D)	Lower lipid targets: 58% 2-3 g/kg/d for infants, 73% 1-2 g/kg/d for older children
PN - lipid emulsions	No evidence supporting the advantage of any of the lipid emulsions. (GOR D)	Most teams routinely used soybean/medium chain triglycerides/olive/fish oil.
PN - composition	Standard PN mixtures usually not suitable for long-term PN in infants and young children. (GOR D) PN solutions providing macro- and micronutrients should be adjusted to individual patient needs. (GOR D)	HPN was provided pharmacy-customised, age-weight specific in 78% of the teams.
Cycling PN	May be used from 3 to 6 months of age (GOR C)	Cycling of PN was mostly based on stable glucose levels, but also on having an older age, weight, enteral intake and a combination of these factors.
Training of parents	By a structured teaching and training programme, conducted by a nurse from the HPN centre's nutrition support team. (GOR D)	Parents were mostly trained by hospital nurses, with a training duration between 1 and 4 weeks.
Vascular access	PICC's and tunneled CVC's should be used in neonates and children receiving long-term PN. (GOR C)	Almost all teams used tunneled CVC's as their first choice. PICC's was standard practice in 7% of teams.
Occlusion of CVC	Urokinase or alteplase for suspected blood deposits and ethyl alcohol and hydrochloric acid for suspected lipid or drug deposits. (GOR D)	97% had a standard procedure, consisting of: urokinase (66%), heparin lock (19%) and alteplase (17%). Other medication used: sodium hydroxide, streptokinase, 70% ethanol and hydrochloric acid.
Prevention of catheter-related occlusion/ thrombosis	Vitamin K antagonists or LMWH may be given prophylactically to patients on long-term PN at risk of or with previous thrombo-embolism. (GOR B)	46% of the teams used anticoagulation: LMWH (standard in 14%, sometimes in 19% of the teams), heparin lock (standard in 12%, sometimes in 17% of the teams), vitamin K antagonists (standard in 2% and sometimes in 14% of the teams) (multiple answers per team possible). Main reason not to give anticoagulation: no evidence.

Table 5. Overview of recommendations by ESPGHAN/ESPEN and clinical practice based on the present survey (continued)

Element	ESPGHAN/ESPEN (2005) [1] - PN in infants, children and adolescents	Survey - practices of IF teams
Removal of CVC	CVC should be maintained until the child is on full EN. (No GOR)	CVC was removed a median of 12 weeks (range 1-26 weeks) after reaching full EN.
Nutritional assessment	Regular monitoring of growth and body composition. (GOR D) Regular measurements of height, weight, and head circumference (<3 years). (LOE 4)	Measurement of weight (100% of teams), height (98%), blood parameters (92%), head circumference (81%), BMI (70%), upper arm/calf circumference (48%), skinfold thickness (34%) and dual energy X-ray absorptiometry (31%).
Monitoring bone health	Regular assessment of bone mineralisation. (GOR D) Bone densitometry: 6 m-1 y interval. (No GOR)	Bone densitometry was used yearly by 32% of teams, never used by 19% of the teams.
Monitoring micronutrients	Periodically monitoring of trace elements. (GOR D) Zinc: 1-3 month interval, vitamin A, E and D: 6 months-1 y interval. (No GOR)	Zinc was measured every 3 months by 41% of the teams. Vitamin A, E and D were monitored with varying frequency ranging from 3 monthly – yearly.
Type of EN	In newborn infants with SBS: breast milk to optimise adaptation. (No GOR) Children with a primary gastrointestinal disease usually require a specific formula when weaning. (GOR D)	Breast milk was recommended in neonates in 88% of the teams. In older children, solid oral feeding was recommended by 56% of the teams.
Mode of EN	EN can be introduced as liquid EN continuously infused over 4 to 24 h. (GOR D) Liquid EN can be given as bolus or sip feeds (orally or artificially). (GOR D) Whenever possible small volumes of oral feeds should be maintained. (GOR D) Bolus feeds or continuous feeding both possible, decision by an expert gastroenterology team. (No GOR)	EN was given as a combination of intermittent and continuous feeding by 44% of the teams, and as oral bolus feeding by 37% of teams. 14% of teams gave EN as continuous feed.

Legend: GOR and LOE according to the Scottish Intercollegiate Guideline Network (SIGN) are defined in **Supplementary Table 3**.
Abbreviations: BMI, body mass index; CVC, central venous catheters; EN, enteral nutrition; GOR, grade of recommendations; HPN, home parenteral nutrition; IF, intestinal failure; LMWH, low molecular weight heparin; LOE, levels of evidence; NA, not applicable; PICC's, peripherally inserted central catheters; PN, parenteral nutrition.

DISCUSSION

The results of our European survey show that there is a large diversity in the composition of paediatric IF teams and the number of patients they are treating. When compared to the current ESPGHAN/ESPEN guideline[1] clinical practice that differed most were lipid targets, the type of catheter lock solution, prophylactic anticoagulation, and monitoring of bone health. In addition, the use of specific medication and the monitoring of psychomotor development were not mentioned in the guideline, but varied widely between the teams.

Regarding the composition of paediatric IF teams, our survey shows that only 46% of teams followed the recommendation of the ESPGHAN/ESPEN guideline[1] and consisted of a physician, pharmacist, nurse, dietician, social worker and psychologist. Previously, it has been shown that treating these children in multidisciplinary teams reduces complications and improves outcome[2-4] and that the risk of death is increased by the absence of a specialist team.[5] When comparing smaller (≤ 10 patients on HPN) versus larger teams (>10 patients), the only member less often present in smaller teams was the dietitian. Next to the composition of IF teams, the number of patients cared for by individual IF teams also varied widely. This variation has been reported previously in the United Kingdom[6,7] and might be due to geographic and organisational reasons, for example the resources available to provide HPN for newly presenting patients.

In general, many similarities between the clinical practice of the teams and the ESPGHAN/ESPEN guideline[1] were found. Beforehand, we hypothesised that the most prominent differences would occur in the areas with the weakest evidence. Our results show, however, that also many similarities were found in these specific areas. The most striking difference between the different teams was the medication routinely used. For example somatostatin analogues were routinely used by 14% of the teams and probiotics by almost half the teams. In addition, half the teams used anticoagulation in the prevention of catheter-related thrombosis or occlusion. Lack of studies about the use of these specific medications most likely explain the variation in clinical practice. Although, limited evidence is available for probiotics[8-11], somatostatin analogues[12-14], A2-adrenergic receptor agonists[15-17] and growth factors[18-22], no directions for clinical use can be given so far and larger intervention studies are definitely needed.

In contrast, prophylactic catheter lock solutions were used by almost all teams. The type of catheter lock solution, however, differed widely, which was also previously reported in a survey among Belgium centres.[23] This might also be explained by financial reasons, since not all catheter lock solutions are reimbursed in every country. In the current guideline nothing is stated about catheter lock solutions, since most research regarding lock solutions has been published after the publication of the current guideline.[24-28]

Since long term PN administration is associated with complications such as low bone mineral density[29,30] and micronutrient deficiencies[31,32], the guideline recommends regular monitoring of bone health and micronutrient status.[1] In contrast to the guideline, bone densitometry was never performed by 19% of the teams, whereas micronutrients such as aluminium and vitamin B12 were not monitored by all the teams.

Another variation in practice when compared to the ESPGHAN/ESPEN guideline[1] was the use of lower parenteral lipid targets. Although not particularly assessed in this survey, this may reflect the increased awareness of possible development of intestinal failure associated liver disease. Most teams routinely used a multicomponent lipid emulsion (SMOF®), in accordance with the ESPGHAN Committee on Nutrition Position Paper that has been published since the guideline.[33]

Ultimately, it is desirable for all children to have a good quality of life and to grow up as normal as possible. According to the survey, in most teams children went to regular schools, sometimes with extra assistance. It is, however, notable that in only half of the teams neuropsychological and psychomotor development was standardly assessed. A recent study showed that children with IF might be at risk of developmental delay[34], emphasizing the importance of neurodevelopmental follow-up.

Our study had some limitations. No response rate could be calculated, since it is unclear which European centres have a paediatric IF team. Therefore it is unknown how many teams did not participate. We have sent an invitation to the survey to a minimum of 45 paediatric IF teams and also received some responses from other teams not directly invited by us. Since all teams involved in the ESPGHAN Network for IF and Transplantation have completed the survey and additionally also smaller teams, we believe that a rather complete overview of paediatric IF care in Europe is provided.

Another limitation is that the guideline from 2005 is not very recent and that clinical practice may have changed since then. Currently, the ESPGHAN/ESPEN is working on a new PN guideline in children, including one chapter on HPN. However, from personal communication with the authors we know that the recommendations in this guideline will only slightly be different and the new guideline will therefore not lead to different conclusions. Next to this, this study describes the compliance with the current guideline, but does not describe actual outcome measures as a quality index. For example, no information is provided regarding the actual nutritional status of the children on HPN, neither on their quality of life, or the number of children able to wean off PN. It was beyond the scope of this survey to relate individual practices to patient outcomes. For example it could be that certain practices might increase the risk of complications. Other practices such as the method of feeding might have an effect on how quickly a child can be weaned off PN. Finally, the heterogeneity of the population of children with IF

may have caused difficulties with completing some questions. The treatment is highly individualised: some questions required an unambiguous answer and only the most applicable answers were provided.

In conclusion, our study is the first to assess organisation and clinical practices of paediatric IF teams in relation to the current guideline. We conclude that wide diversity exists in the organisation of paediatric IF teams and in the clinical practice of these teams in terms of medication and monitoring of long-term complications. To improve the quality of care and optimise outcome for children with IF, there should be agreement on organisation of IF teams and standards of care. In line with the guideline it should be clear which members should at least be part of the multidisciplinary team. Next to this and because of the complex care needed, it is recommended that teams have enough experience to provide HPN care for children. The need for sufficient experience is an important argument for establishing regional referral centres in areas with multiple teams treating few patients. Regarding topics such as the use of specific medication, experience should be shared. This survey provides valuable information that can be used to develop both practical protocols and recommendations with focus on implementation of the guideline, and to develop new international research collaborations between centres.

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SUPPLEMENTARY DATA

Supplementary data 1: Survey

Part 1. General information

In this first part of the survey, we would like to ask you some general information about your IF team.

What is your email-address?

We need your email-address to make sure that part 1 and part 2 of the survey can be linked. Results of the survey will be analysed anonymously.

1. What is your country of work?
2. What is the name of your institution?
3. What type of hospital do you work in?
   - o General hospital
   - o University hospital
   - o Children's hospital (non-university)
   - o University/teaching-children's hospital
   - o Other: ……
4. What is your profession?
   - o Paediatric gastroenterologist
   - o Paediatric surgeon
   - o Paediatrician
   - o Dietician/nutritionist
   - o Nurse/nurse practitioner
   - o Other: ……
5. How long has your IF team been managing children on home parenteral nutrition (HPN)?
   - o <1 year
   - o 1 – 5 years
   - o 6 – 10 years
   - o 11 – 20 years
   - o >20 years
6. How many years of experience do you have in working in an IF team?
   - o <1
   - o 1 – 5
   - o 6 – 10
   - o 11 – 20
   - o >20

7. Is the paediatric IF team combined with an adult IF team?
   - o Yes
   - o No

8. Where does your IF team consist of? Please fill in the numbers of members and the total numbers of hours per week that they work for the IF team (for example if 2 paediatric surgeons work 5 hours per week for the IF team, fill in 2 and 10 respectively).

Please fill in zero if not applicable.

Profession	Number	Hours per week
Paediatric gastroenterologist		
Paediatric surgeon		
General paediatrician		
Dietician/nutritionist		
Nurse/nurse practitioner		
Pharmacist		
Psychologist		
Social worker		
Speech therapist		
Physical therapist		
Other, please specify in comments		

Patients

9. What is the current number of children (<18 years) on HPN attending your IF team?
10. Please specify the distribution of underlying causes of IF of the children on HPN attending your team.

	Number of children
• Short bowel syndrome:	.....
• Motility disorder:	.....
• Enteropathy:	.....

11. Please specify the age categories of children on HPN attending your team.

	Number of children
• Neonates (0 – 1 month):	.....
• Infants (1 month – 1 year):	.....
• Children (1 – 5 year):	.....
• Children (5 – 10 year):	.....
• Children (10 – 15 years):	.....
• Adolescents (>15 years):	.....

12. Does your IF team also continue monitoring children weaned off HPN?
    - o Yes
    - o No

- *If yes, please go to question 14*
- *If no, please go to question 15*

13. What is the current number of children (<18 years) weaned off PN attending your team?
14. Do you have anything to add to this survey?

Part 2

What is your email-address?

To make sure part 1 and part 2 of the survey are linked to the same person, we ask you to fill in your email-address. Results of the survey will be analysed anonymously.

Vascular access

1. What kind of central venous line do you use for the administration of HPN?

	Standard	Sometimes	Never
Central venous catheter – tunneled (for example Broviac® or Hickmann®)			
Central venous catheter – untunneled			
Peripheral inserted central catheter (PICC)			
Port-a-cath			
Other, please specify in comments			

2. Do you use catheter lock solution(s) other than normal saline?
    - o Yes
    - o No

If yes:

What kind of catheter lock solution(s) is/are used?

	Standard	Sometimes	Never
Taurosept® (taurolidine)			
Taurolock™ (taurolidine and citrate)			
Ethanol			
Heparin			
Other, please specify in comments			

If no:

Please explain why catheter lock solution(s) are not used by your IF team.

3. Do you use anticoagulation in the prevention of catheter-related thrombosis/occlusion?
    - o Yes
    - o No

If yes:

What type of anticoagulation?

	Standard	Sometimes	Never
Low molecular weight heparin (for example nadroparin)			
Vitamin K antagonists (for example acenocoumarol)			
Heparin lock			
Other, please specify in comments			

If no:

Please explain why anticoagulation drugs are not used by your IF team.

4. Do you have a standard procedure in case of occlusion of the catheter?
   - o Yes
   - o No

If yes:

What do you use in case of occlusion of the catheter?

	Standard	Sometimes	Never
Heparin lock			
Urokinase			
Alteplase			
Other, please specify in comments			

Home parenteral nutrition

5. How is the HPN provided in your institution?
   - o Pharmacy-customized, age/weight specific
   - o Commercial mixed bags
   - o Commercial mixed bags customized by the pharmacy (for example a commercial mixed bag with specific mixture of vitamins and micronutrients by the pharmacy)
   - o Other: …….
6. Which lipid emulsion(s) is/are used for HPN?

	Standard	Sometimes	Never
Soybean lipid emulsions (for example Intralipid®)			
Soybean/medium chain triglycerides (medium-chain triglycerides)/olive/fish oil lipid emulsions (for example SMOFlipid®)			
Fish-oil lipid emulsions (for example Omegaven®)			
Olive/soybean lipid emulsions (for example Clinoleic®)			
Soybean/medium-chain triglycerides lipid emulsions (for example Lipoplus®)			
Other, please specify in comments			

7. Do you use the protein target as described by the ESPGHAN/ESPEN guideline (neonates 1.5-3 g/kg/d, 2 months-3 years 1-2.5 g/kg/d, 3-18 years 1-2 g/kg/d)?
   - o Yes
   - o No, please specify in comments what protein target is used by your IF team
   - o Unknown
8. A) What do you in general use as parenteral lipid target for infants and young children?
      - o 1-2 g/kg/day
      - o 2-3 g/kg/day
      - o 3-4 g/kg/day
      - o Unknown
      - o Other, please specify: ……
   B) What do you in general use as parenteral lipid target for older children?
      - o 1-2 g/kg/day
      - o 2-3 g/kg/day
      - o 3-4 g/kg/day
      - o Unknown
      - o Other, please specify: ……
9. In children on full PN, how many days/nights do you prescribe the lipids?
   - o All days
   - o 5-6 days
   - o Less than 5 days
   - o Other, please specify: ……
10. What is the maximum (parenteral) amount of carbohydrates used?
    - o 16 g/kg/day
    - o 18 g/kg/day
    - o 20 g/kg/day
    - o Unknown
    - o Other, please specify: ……
11. Which criteria do you use to decide whether cycling of the PN is possible (for example a certain age or weight of the patient)?
12. Who pays for the PN?
    - o Health insurance
    - o Hospital
    - o Unknown
    - o Other, please specify: ……
13. In general, who administers the HPN?
    - o Parents/caregivers
    - o Home care companies

- o Other, please specify: ……

If parents/caregivers:

Who trains the parents/caregivers to administer the HPN and take care of the central venous line? And how much time does this training take?

Enteral/oral nutrition

14. What type of feeding is recommended when nutrition is started in neonates/infants?

A) For neonates/infants:

	Standard	Sometimes	Never	Unknown
Human milk				
Polymeric (containing whole protein, complex carbohydrates and long-chain triglycerides)				
Oligomeric (containing protein hydrolysates, complex carbohydrates and medium-chain triglycerides)				
Monomeric (containing amino acids, complex carbohydrates and long-chain triglycerides)				

B) For older children:

	Standard	Sometimes	Never	Unknown
Polymeric (containing whole protein, complex carbohydrates and long-chain triglycerides)				
Oligomeric (containing protein hydrolysates, complex carbohydrates and medium-chain triglycerides)				
Monomeric (containing amino acids, complex carbohydrates and long-chain triglycerides)				
Solid oral feeding				

15. How is the enteral nutrition most often administered?
    - o Intermittent/bolus feeding (for example 6 feedings of 120 ml) – orally
    - o Intermittent/bolus feeding (for example 6 feedings of 120 ml) – by tube
    - o Continuous (for example continuous tube feeding of 30 ml per hour)
    - o Combination of intermittent and continuous feeding (for example 20 hours tube feeding of 30 ml per hour with 2 times a bottle of 60 ml)
16. When is on average the central venous line removed after reaching full enteral nutrition (i.e. after how many days/weeks/months)?
17. Is a speech therapist involved in the introduction of oral feeding?
    - o Yes
    - o No

Nutritional status/bone health

18. How is nutritional status monitored regularly?
    - o Weight
    - o Height
    - o Head circumference
    - o BMI
    - o Upper arm/calf circumference
    - o Skin fold thickness
    - o Dual Energy X-ray Absorptiometry
    - o Air displacement plethysmography
    - o Other, please specify: ……

19. On average, how often do you measure micronutrient levels?

Never – Every 3 months - Every 6 months – Yearly – Every 2 years – >2 years interval – Unknown

- o 25-OH vitamin D
- o Vitamin A
- o Vitamin E
- o Vitamin B1
- o Vitamin B2
- o Vitamin B6
- o Active vitamin B12
- o Total vitamin B12
- o Zinc
- o Aluminium
- o Copper
- o Chromium
- o Selenium
- o Manganese

20. How do you monitor bone health in children with IF? And how often?

Never – Every 6 months – Yearly – Every 2 years – >2 years interval – Unknown

- o Blood parameters (for example calcium, phosphate, vitamin D)
- o Dual energy X-ray absorptiometry
- o Digital X-ray radiogrammetry (X-ray of the hand with use of the BoneXpert software)

Surgery/medication

21. Which of the following procedures are performed in your centre?
    - o Serial transverse enteroplasty (STEP)
    - o Bianchi procedure

- o Intestinal transplantation
- o None of these procedures

22. What is the frequency of the procedures performed?
    Number of procedures/year
    - o Serial transverse enteroplasty (STEP)
    - o Bianchi procedure
    - o Intestinal transplantation

Please fill in zero if not applicable.

23. Which of the following medication do you use regularly for children on HPN?
    - o Histamine receptor antagonist (e.g. ranitidine)
    - o Proton pomp inhibitor (e.g. omeprazole)
    - o A2-adrenergic receptor agonist (e.g. clonidine)
    - o Somatostatin analogue (e.g. octreotide)
    - o Antidiarrheal/antimotility agents (e.g. loperamide)
    - o Bile acid sequestrant (e.g. cholestyramine)
    - o Prokinetic agents (e.g. erythromycin)
    - o Antibiotics as treatment for small intestinal bacterial overgrowth (e.g. metronidazole)
    - o Probiotics
    - o Growth factors (e.g. Glucagon-like peptide-2 analogue teduglutide)
    - o Other: ……..

Neuropsychological and psychomotor development/general questions

24. In general, how do the children on HPN treated by your team perform on an intellectual level when they go to elementary school?
    - o Most of them go to regular schools
    - o Most of them go to regular schools with extra assistance
    - o Most of them go to special needs schools (due to medical reasons)
    - o Most of them go to special needs schools (due to intellectual reasons)

Please enter your comment here

25. Is neuropsychological and psychomotor development standardly assessed in your IF team?
    - o Yes
    - o No

26. Do you have anything to add to this survey?

SUPPLEMENTARY DATA 2

Supplementary Table 1. Frequency of micronutrient monitoring among IF teams

Number of IF teams / N (%) Micronutrient	Every 3 months	Every 6 months	Yearly	Every 2 years	>2 years	Never	Unknown
25-OH vitamin D	32 (54)	21 (36)	6 (10)	NA	NA	NA	NA
Vitamin A	24 (41)	26 (44)	9 (15)	NA	NA	NA	NA
Vitamin E	26 (44)	23 (39)	9 (15)	NA	NA	1 (2)	NA
Vitamin B1	8 (14)	8 (14)	11 (19)	1 (2)	2 (3)	26 (44)	3 (5)
Vitamin B2	8 (14)	7 (12)	10 (17)	1 (2)	2 (3)	28 (48)	3 (5)
Vitamin B6	11 (19)	9 (15)	12 (20)	1 (2)	2 (3)	22 (37)	2 (3)
Active vitamin B12	7 (12)	10 (17)	8 (14)	NA	2 (4)	27 (46)	5 (9)
Total vitamin B12	26 (44)	17 (29)	13 (22)	NA	1 (2)	2 (3)	NA
Zinc	24 (41)	24 (41)	8 (14)	NA	NA	3 (5)	NA
Aluminium	4 (7)	8 (14)	8 (14)	NA	4 (7)	28 (48)	7 (12)
Copper	17 (29)	18 (31)	10 (17)	1 (2)	2 (3)	8 (14)	3 (5)
Chromium	4 (7)	3 (5)	8 (14)	1 (2)	3 (5)	32 (54)	8 (14)
Selenium	16 (27)	16 (27)	11 (19)	1 (2)	1 (2)	13 (22)	1 (2)
Manganese	10 (17)	8 (14)	11 (19)	1 (2)	3 (5)	25 (42)	1 (2)

Legend: Values expressed as N (%).
Abbreviation: NA, not applicable.

Supplementary Table 2. Frequency of bone health monitoring among IF teams

	Every 6 months	Yearly	Every 2 years	>2 years interval	Never	Unknown
Blood parameters	56 (95)	2 (3)	1 (2)	NA	NA	NA
Dual energy X-ray absorptiometry	1 (2)	19 (32)	10 (17)	14 (24)	11 (19)	4 (7)
Digital X-ray radiogrammetry (X-ray of the hand with use of BoneXpert software)	1 (2)	4 (7)	4 (7)	5 (9)	37 (63)	8 (14)

Legend: Values expressed as N (%).
Abbreviation: NA, not applicable.

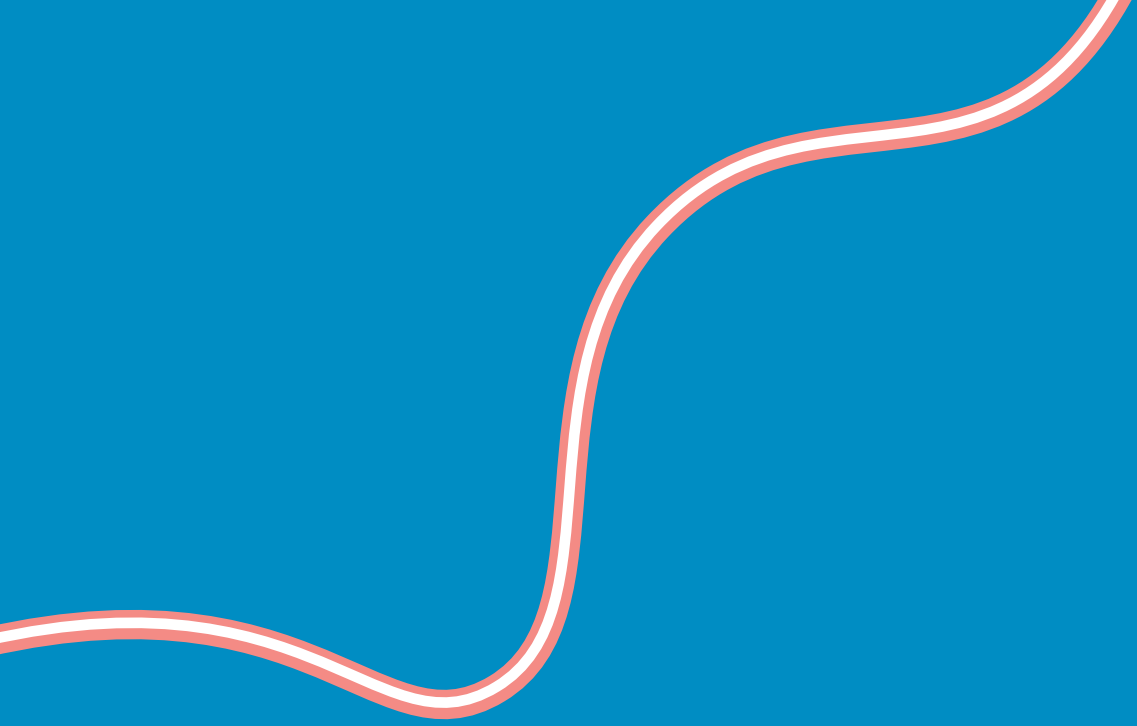
Supplementary Table 3. Grading of levels of evidence (LOE) and grading of recommendations (GOR) according to the Scottish Intercollegiate Guideline Network (SIGN) 2000.

Level of evidence	Study design	Special conditions	Grading of recommendation
1++	High quality meta analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.	If directly applicable to target population.	A
		Extrapolated evidence.	B
1+	Well conducted meta analyses, systematic reviews of RCTs, or CTs with a low risk of bias.	If directly applicable to target population and overall consistency of results.	A
		Extrapolated evidence.	B
1-	Meta analyses, systematic reviews of RCTs, or RCTs with a high risk of bias.		No supporting recommendation
2++	High quality systematic reviews of case-control or cohort studies. High quality case-control or cohort studies with a very low risk of confounding, bias, or chance, and a high probability that the relationship is causal.	If directly applicable to target population and demonstrating overall consistency of results.	B
		Extrapolated evidence.	C
2+	Well conducted case control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal.	If directly applicable to target population and demonstrating overall consistency of results.	C
		Extrapolated evidence.	D
2-3	Case control or cohort studies with a high risk of confounding, bias, or chance, and a significant risk that the relationship is not causal.		No supporting recommendation
3	Non-analytic studies, e.g. case reports.		D
4	Expert opinion.		

Abbreviation: RCT, randomized controlled trial.

PART III

DISCUSSION AND SUMMARY



12

General discussion

Children with intestinal failure (IF) are dependent on long-term parenteral nutrition (PN). Until 15 years ago, the prognosis of these children was poor. Over the past few decades, however, survival of children with IF has improved significantly with better quality of surgical treatment, neonatal care, and treatment advancements such as improved PN and the use of catheter lock solutions to prevent central venous catheter related blood stream infections. This improved survival has made the long-term outcomes increasingly important. While complications such as line sepsis and liver failure are less common than before, long-term morbidities of IF such as poor bone health, abnormal body composition and psychosocial problems may arise. These are currently not well explored. Our aims were therefore to study outcomes of children with IF – with focuses on growth, body composition, bone health, the gut microbiota and parental quality of life. In addition, we evaluated the costs of treatment and organizational aspects important in the care of these patients. The studies' most important conclusions are shown in **Figure 1.** Additionally, we provided an overview of the best nutritional strategies and medication that promote intestinal adaptation in **Chapter 2**. Below, we discuss the main findings of our studies and relate these to the current literature. We also provide recommendations for future research and implementation of our findings in clinical practice.

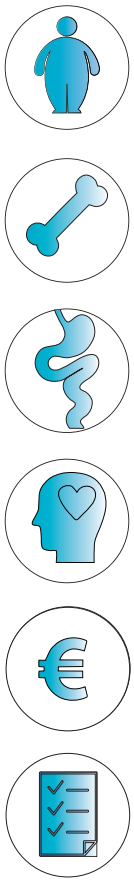
MORBIDITIES RELATED TO INTESTINAL FAILURE

Growth failure

The studies presented in **Chapters 3, 4 and 5** dealt with growth of IF patients. We found that children with IF were significantly shorter and lighter than healthy references one year after the start of PN. Patients who were long-term PN dependent were also shorter and lighter. Abnormal growth was not only commonly found during the treatment with PN, but also after weaning off PN. We described the course of growth longitudinally, showing catch-up growth during PN but a decrease of height-for-age after weaning. In contrast, the course of weight-for-age was not different during versus after weaning off PN.

Of the growth parameters, height was impaired most. Between 17% and 33% of the children had a height-for-age standard deviation score (SDS) below -2, defined as chronic malnutrition. It is important, however, to not only evaluate height-for-age, but also assess growth to target height. The target height is based on the parental heights and reflects the genetic determinant influencing growth.[1,2] The median distance between height-for-age SDS and target height SDS was negative, indicating that children with IF are growing less well than expected based on their genetic potential. Moreover, between 9% and 52% of the children (depending on the study population) were growing below their target height range.

Figure 1. Overview of main findings regarding the outcomes of patients with intestinal failure, and the evaluation of costs and organizational aspects of care based on the studies described in this thesis



Growth	Patients with IF were significantly shorter and lighter than healthy references when on PN Catch-up growth during PN, decrease of height-for-age after weaning Up to 50% of the children was growing below target height range
Body composition	Lower fat free mass and higher fat mass than healthy references during PN When weaned off, lower fat free mass than healthy references
Micronutrients	Frequent micronutrient deficiencies, especially of fat-soluble vitamins, during PN and after weaning
Bone health	Up to 50% of IF patients had poor bone health Lower bone mineral density than healthy references, both during PN and after weaning
Microbiota	IF patients had altered metabolic activity and lower bacterial diversity and richness compared to healthy controls Increased relative abundance of Proteobacteria, decreased relative abundance of Firmicutes and Bacteroidetes in IF patients Surgical IF patients had lower bacterial diversity than functional IF patients Nutritional characteristics were associated with microbial diversity and variation in the microbiota
Parental quality of life	Parents of children on home PN reported normal health-related quality of life Mothers higher levels of depression compared to reference mothers Both fathers and mothers more distress than reference parents
Costs	High anual costs, especially for the first year Costs mainly included hospital admissions and PN Intestinal rehabilitation is cost-effective
Survey	Wide diversity of composition of IF teams and numbers of patients treated Good compliance to exisiting guideline Clinical practice that varied most was standard use of medication & monitoring of long-term complications

Abbreviations: IF, intestinal failure; PN, parenteral nutrition.

Poor growth in terms of lower weight and height has been reported previously, similar to that in our cohort.[3-8] However, the proportion of patients with chronic malnutrition in our study was lower than that in previous research[3], which might be due to the fact that part of the children included in our studies were already weaned off PN, implying less severe IF. Another explanation might be the lower proportion of children with an enteropathy included in our studies**,** whereas in the previous study patients with an enteropathy were more often diagnosed with chronic malnutrition.[3] Strikingly, most previous studies did not take into account the child's target height. The fact that previous studies did not describe a decrease in height after weaning might be explained by the limited follow-up period after weaning off PN in these studies.[9,10] In contrast, another study evaluating growth only in patients weaned off PN also found poor growth.[4]

The cause of growth failure in IF seems to be multifactorial, but studies – including our study – show non-conclusive results. Several factors influencing growth have been described.[3] In infants with short bowel syndrome, having necrotizing enterocolitis and two or more central-line associated bloodstream infections were independent risk factors for stunted growth.[10] Although we could not identify reasons for poor growth, the nutritional intake may have been too low to achieve optimal growth. Our results, showing that height-for-age, but not weight-for-age decreased after weaning, suggest that patients weaned off PN receive enough oral and/or enteral nutrition to maintain their weight growth, but may suffer from persistent chronic malabsorption. Consequently, they might need more nutrition (either enteral or parenteral) to maintain their linear growth course. On the other hand, in clinical practice it is often seen that higher nutritional intake does not necessarily lead to improvement of linear growth, but to disproportional weight gain. When looking at the estimation of nutritional requirements, previous studies reported conflicting results about the total and resting energy expenditure in children with IF.[11,12] Another factor that might influence growth is prematurity, although we found that abnormal growth was not only common in premature born infants, but also in term born infants. Moreover, most of the premature born infants in our study were not very preterm, but born after a gestational age of 32 weeks. Most previous studies did not investigate the contribution of prematurity to poor growth of pediatric IF patients. Next to this, certain enteropathies may be associated with short stature.[13,14] Additionally, alterations in levels of insulin-like growth factors may play a role. A previous study reported elevated insulin-like growth factor 1 levels[15], although also low levels of insulin-like growth factor 1 and insulin-like growth factor binding protein 3 have been described.[16] Chronic intestinal inflammation may also influence growth, for example due to small intestinal bacterial overgrowth. One previous study did not support this possibility, as controls and IF patients had comparable levels of pro-inflammatory cytokines.[15] Since we do not routinely measure these cytokines or perform gastro-intestinal endoscopies to evaluate intestinal inflammation, the current best surrogate marker known is calprotectin. In **Chapter 7** we showed that most of our patients on home PN (HPN) had calprotectin levels below detectable levels and therefore we were not able to link this to poor growth.

As survival of patients with IF was poor until 15 years ago, little is known about nutritional status and growth of patients with IF during puberty. It might be that an increase, or if weaned off a restart, of PN is needed to achieve adequate growth. A previous study reported that this increase or restart resulted in minimal height increase, but substantial weight gain and pubertal development.[17] To ensure timely intervention if necessary, growth including pubertal development should be evaluated regularly. Future studies evaluating growth should also focus on growth and nutritional needs in this specific period.

Abnormal body composition

Information about body composition (fat mass and fat free mass) in patients with IF is scarce. In clinical practice, weight-for-height and BMI are often used as proxy markers for body composition. However, we showed that these growth parameters were not significantly different from those in healthy references (**Chapter 4**). In contrast, we showed that children with IF receiving long-term PN have significant abnormalities of body composition with lower fat free mass and higher fat mass than healthy references after correction for their smaller body size. Even when weaned off PN, patients with IF had a significant lower fat free mass measured by dual energy X-ray absorptiometry (DEXA, **Chapter 3**).

The lower fat free mass is more or less in agreement with previous studies in children on HPN, depending on the method used[4,6,11], while these studies reported normal fat mass or a higher fat mass only in totally PN-dependent patients.[6,11]

Abnormal body composition in patients with IF may be a consequence of excessive energy intake and potential overfeeding, although PN prescriptions take into account age, activity level and routine growth parameters. In our study we did not find any association between parenteral intake (either caloric or macronutrient intake) and body composition. Another factor that may be important is less physical activity. In a previous study showing normal fat free mass, accelerometry indicated similar levels of physical activity compared to healthy controls.[11] Although we did not properly assess physical activity, and most patients could engage in common daily activities including sports, our clinical experience is that they may be less active than healthy children.

The fact that weight-for-height and BMI were not different from healthy references, suggests that frequently used parameters are not valid in assessing body composition. It is therefore advised to measure body composition to be informed about the fat free mass and fat mass. This can be done with various methods, including DEXA – as described in **Chapter 3** – and air displacement plethysmography – as described in **Chapter 4**. The advantages of the latter method include the fact that additional devices such as the central venous catheter or enterostomy bag can be calibrated and therefore do not interfere with the measurement, as well as the possibility to measure body composition already from neonatal age onwards. We showed that air displacement plethysmography is a feasible method to measure body composition in infants and children with IF.

Evaluating body composition is of importance since abnormal body composition can be associated with several determinants of cardio metabolic health on the long term.[18-21] In addition, fat free mass is essential for developing bone mass.[22,23] From previous research in healthy term born infants, the first three months of life have been identified as a critical window.[24,25] One can imagine that this holds as well for children with IF who often receive all or most of their calories via PN. Body composition should therefore preferably be

measured from birth onwards. Monitoring should not only be performed during PN, but also be continued after weaning off PN.

Micronutrient deficiencies

We showed in **Chapter 3** that micronutrient deficiencies were common both during PN and after achieving intestinal autonomy. This is in agreement with previous studies, although we found a somewhat higher prevalence of abnormalities of micronutrients.[26-30]

Generally, it is assumed that micronutrient preparations in PN meet the nutritional requirements for totally PN-dependent patients. We found deficiencies, however, in totally PN-dependent children, suggesting that the micronutrient supplementation in PN should be reevaluated. Deficiencies during/after weaning off PN might be due to enteral malabsorption. Especially fat-soluble vitamins such as vitamin A, E and 25-OH vitamin D were frequently deficient, which might be caused by fat malabsorption due to ileal resection, cholestasis or the use of cholestyramine.

Strikingly, not all micronutrients were regularly monitored according to a strict protocol and this inconsistency could be improved in clinical practice as well for future research.

Poor bone health

Another complication of IF is poor bone health.[3,27,31,32] We found that up to 50% of the children with IF have a low bone mineral density (BMD) and that children with IF have significantly lower BMD than healthy references (**Chapter 5**). Poor bone health was also common after weaning off PN, which was also demonstrated by other authors.[4,32]

A low BMD and subsequent lower peak bone mass are risk factors for osteoporosis and bone fractures later in life.[33,34] In our population, three children developed multiple fractures; two of them were diagnosed with osteoporosis, while this was highly suspected in the third (**Addendum Chapter 5**). After receiving bisphosphonates, two of these patients did not develop any new bone fractures and no serious side effects during the treatment of bisphosphonates were seen. However, bisphosphonates should only be given when there is a strong indication, since they might inhibit the growth plate activity.[35]

The pathophysiology of poor bone health is multifactorial. In our study, we found that age and duration of PN as well as having surgical IF had a significant negative influence on BMD Z-scores at the first DEXA scan around the age of 6 years. In addition and against our expectation, higher weight-for-height Z-scores were related to lower BMD Z-scores. This might be explained by the fact that children with a higher weight-for-height have lower height-for-age Z-scores (poorer growth), and are therefore inappropriately diagnosed with low BMD because they are compared with age-matched controls and not height-matched controls. Less physical activity might be another important factor

for poor bone health in children with IF. Plyometric exercise has been shown to improve bone mineral content and density.[36] Moreover, muscle mass is important to develop bone mass.[22,23,37] Although we evaluated both bone health and body composition, we were not able to relate these outcomes since these measurements were not performed at the same time. Next to muscle mass, vitamin D intake is important for good bone health, although in our study vitamin D deficiency based on serum 25-OH vitamin D, was not a significant predictor of BMD Z-scores, in agreement with a previous study.[38]

The current golden standard to monitor bone health is with DEXA by measuring BMD of the total body (BMD_{TB}) and lumber spine (BMD_{LS}). The most important limitations of this method are the lack of reference values below 4 years of age and the fact that it does not directly adjust for poor growth/small body size. Since poor bone health is also seen in younger children with IF (**Addendum Chapter 5),** there is a need for other methods of assessing bone health in this population. We compared DEXA with hand radiogrammetry which is a relatively new and non-invasive and practical method. It uses hand radiographs with special software called BoneXpert® with reference values available for children ≥ 2.5 years of age.[39] We found that the agreement between these methods was good for diagnosing low BMD, as defined as Z-scores ≤ -2 by the International Society for Clinical Densitometry. This suggests that hand radiogrammetry may be used for monitoring bone health in children with IF, although these results need to be confirmed in larger prospective studies. No other studies using hand radiogrammetry in children with IF have been performed so far. However, the low costs and the fact that these hand radiographs are already part of routine growth work-up in children with IF, and therefore do not expose them to additional radiation, make this method very feasible.

Besides the availability of reference values for young children, another important advantage of hand radiogrammetry is that it directly adjusts for bone age and therefore for impaired growth. In children with growth failure, the BMD_{LS} is underestimated because of their smaller bone size. Comparison with healthy age references with normal height will therefore lead to lower Z-scores for BMD_{LS}. DEXA Z-scores can be corrected for poor growth in different ways: by using the bone mineral apparent density, by using the height age instead of the calendar age to calculate the BMD Z-scores and by correcting the BMD Z-scores for bone age. In **Chapter 5** we showed that using the bone mineral apparent density and height age corrected BMD Z-scores reduced the number of children inappropriately diagnosed with low BMD. However, these analyses are currently mainly used for research purposes and their clinical value is not yet known and should therefore be addressed in future studies.

Altered gut microbiota

Chapter 6 reviewed what is known about the gut microbiota in adults and children with IF based on previously published research. Following this literature review, we concluded that patients with IF have remarkably reduced gut microbiota diversity**.** Next to this, community structure is altered with an overabundance of Proteobacteria, especially of the Enterobacteriaceae family. Gut microbiota characteristics have been associated with poor growth, liver disease, small intestinal bacterial overgrowth, risk of D-lactic acidosis and duration of PN.[40-45] In addition, some studies reported differences between patients on PN and patients able to wean off PN, although this was not the primary aim of these studies.[40,41,45,46] Most of these studies were cross-sectional and did only include patients with surgical IF. Additionally, very limited data is available about the metabolic activity of the gut microbiota in patients with IF.[42]

Therefore, we aimed to assess the microbiota including its metabolic activity in children with IF on long-term PN in a longitudinal way (**Chapter 7**). Similar to the previous studies, we found markedly reduced bacterial diversity, richness and evenness, all presumptive markers of optimal gut health. Patients with IF had a higher relative abundance of Proteobacteria, whereas their abundance of Firmicutes and Bacteroidetes was decreased. Proteobacteria normally represent only a very small fraction of the gut microbiota and many species belonging to Proteobacteria are potentially opportunistic pathogens, including *Cronobacter* and *E. coli*.

Changes in gastro-intestinal anatomy and physiology are thought to be the main factors contributing to the changed microbiota, leading to proliferation of aerobic bacteria at the expense of anaerobic bacteria. Extensive small bowel resection in the children with short bowel syndrome, for example, may lead to a lower luminal pH, increased oxygen concentration, disruption of the enterohepatic bile acid circulation, a rapid transit time and a large amount of undigested nutrients presented to the remaining colon.[47-50] Indeed in our study we observed differences between patients with surgical IF and those with functional IF having their whole gut in situ; functional IF patients had a microbial community structure more similar to healthy controls, and had a higher bacterial diversity and a lower abundance of taxa belonging to Lactobacillus and Cronobacter. It is difficult to compare these results with previous studies, since only one study also included functional IF patients but did not compare these two different groups.[41]

The lack of luminal fermentable substrate necessary for growth of anaerobic bacteria, such as fiber and resistance starch, is another important factor that might explain the decrease in Firmicutes and Bacteroidetes. The decrease of these phyla, known as main fiber fermenters and short-chain fatty acid producers, was also illustrated by lower concentrations of total and most individual short-chain fatty acids compared to healthy controls. This is in contrast with one previous study including infants with short bowel

syndrome, showing only differences in fecal acetate concentration.[42] Short-chain fatty acids have several important roles in the human body, including increase of sodium absorption and growth inhibition of potentially harmful bacteria, and growth promotion of beneficial bacteria.[51-53] More important, they are used as a source of energy.[54,55] In contrast, patients in our study had higher concentrations of D- and L-lactate than healthy controls, which is probably caused by increased abundance of lactate producing bacteria and decreased abundance of lactate consuming bacteria.[55-57]

Important clinical factors related to variation in the microbiota were duration of PN, percentage of calories provided by PN and oral/enteral fiber intake. The percentage of calories provided by PN, often used as a marker for PN dependency, was negatively associated with microbial diversity. Korpela et al.[41] also found that duration of PN and PN calories were related to variation in the microbiota. Other studies did not evaluate these clinical factors, but mostly focused on differences in the microbiota associated with poor growth[40] or diarrhea.[58] Moreover, previous studies showed that the remaining small bowel length is an important influencing factor.[41,59] In our study, we could not confirm this, probably due to the fact that only 5 patients had short bowel syndrome and only 3 patient had a remaining small bowel length ≤ 50 cm.

During the study period, two patients were able to wean off PN. Interestingly, the microbial diversity increased and the microbial structure appeared to move closer to that of healthy controls as the gut adapted and patients could transit from PN to oral/enteral nutrition. Moreover, the percentage of enteral nutrition was negatively associated with the amount of Proteobacteria, in agreement with previous studies.[41,45,46,59] Moreover, selective species such as Bacteroides and Bifidobacterium appeared to bloom in patients whose gut adapted over time. Future research should explore whether these changes precede or follow gut adaptation; hence the role they may play in adjusting clinical practice based on the gut microbiota during this process. The microbiota may also be a therapeutic target, for example by giving more targeted antibiotic, pre-, pro- or synbiotics or supplementation of fiber and this should receive attention in further research.

Parental health-related quality of life and psychosocial morbidity

Next to the medical consequences of IF, it can have profound psychosocial consequences for patients and their families.[60] Parents of children with IF may experience psychosocial problems due to the illness and intensive treatment of their child. These parental psychosocial problems may influence the well-being of the child.[61-63] Therefore, we evaluated the health-related quality of life, levels of anxiety, depression and distress of mothers and fathers of children on HPN. Surprisingly, no differences were found in health-related quality of life between parents of children on HPN and reference parents, except for the subscales 'depressive emotions' for mothers and 'daily activities' for fa-

thers (**Chapter 8**). This might be explained by the fact that practical problems are more dominant in daily life. Previously, only a few studies on this issue have been conducted, often only including mothers or having a qualitative design, which makes a comparison difficult.[64-66] Regarding overall distress, both mothers and fathers reported more distress than did reference parents. Mothers reported more problems in the practical, emotional, cognitive and parenting domains whereas fathers reported more problems in the social domain, and also in the emotional and parenting domains. These findings highlight that healthcare professionals should see the need for structural screening for psychosocial problems in parents of children with IF in order to improve the well-being of both parents and their children dependent on HPN. In addition, more in depth qualitative research can give more insight into specific problems parents experience, which might not be captured by using generic questionnaires.

ORGANIZATIONAL ASPECTS

Since IF is a rare disease, it is of utmost importance to collaborate with other IF teams on a national and international level. This will enable the performance of clinical studies aiming to improve care and outcome of these patients.

To improve standard care of Dutch patients with chronic IF, a nationwide collaboration for patients with IF in the Netherlands had been established in 2013. One of the aims of this collaboration was to obtain recent prevalence data of IF in the Netherlands, since the latest registration had been performed in 2004. Hence, we developed a web-based registry. Registration in this registry provided a more up to date point prevalence of chronic IF of 9.56 for children (**Chapter 9**). The increase in chronic IF patients with HPN might reflect both increasing numbers and increased experience in specialized HPN centers, but also improvement of overall HPN survival rates, as well as previous insufficient documentation. As shown by our registry, only a small number of patients underwent intestinal transplantation (ITx) in the Netherlands. This has also been described by other authors.[67,68] Because of improved survival on HPN and the fact that mortality and graft failure rates after ITx are still high[69], ITx should be only considered in case of life-threatening complications that make treatment with HPN impossible. Using a registry will support multidisciplinary care and decision-making and may be used as a national quality instrument.

Another aim of the national collaboration was to gain more insight into the costs of treatment of pediatric IF. Previous studies have shown that costs of care for children with short bowel syndrome are enormous, but knowledge about costs of children with different types of IF was not available. **Chapter 10** shows that the annual costs of pediatric IF are very high, especially for the first year. Cost-effectiveness analysis was performed by comparing two scenarios: one with intestinal rehabilitation and one without. In the scenario with rehabilitation, a proportion of patients representing those with the ability to wean off PN was assigned to intestinal rehabilitation. In the scenario without rehabilitation, all patients progressed to HPN. In both scenarios, a proportion of patients on HPN was eventually eligible for intestinal transplantation. Intestinal rehabilitation prolonged survival, and was associated with cost savings, and therefore considered to be cost-effective. The bulk of the costs were related to hospital admission, especially the first admission including the start of IF. Another contributor to the high costs was the PN itself, which is mostly individually customized for children by pharmacies and therefore expensive. The high costs add to the motivation to minimize complications due to PN.

Despite the complexity of the treatment of IF, evidence-based guidelines for the treatment of these patients are scarce. Because of improved survival and increased prevalence of HPN it is essential to harmonize and optimize clinical guidelines. As a first step, we provided an overview of the organization and current practice of pediatric IF teams

across Europe (**Chapter 11**). We found that there is a large diversity in the composition of these teams. The ESPEN/ESPGHAN guideline available at time of our study (published in 2005)[70] recommends that a multidisciplinary team should at least consist of a physician, pharmacist, nurse, dietitian, social worker and psychologist. However, according to our survey less than half of the teams did not comply with this recommendation, mainly due to the absence of a social worker or psychologist. The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition recommends that the team should at least include a gastroenterologist, surgeon, dietitian and a nurse.[71] Using this definition, 82% of teams in our survey would comply with the recommendation. Close collaboration with neonatologists is important, as well as with social workers, physical therapists, speech therapists and child psychologists. Next to the composition of the pediatric IF teams, numbers of patients treated also varied widely. This might be due to geographic and organizational reasons (i.e. lack of centralized care), and the available resources.

When looking at clinical practice compared to the ESPEN/ESPGHAN guideline available at time of the study[70], topics that differed most were parenteral lipid amounts, the type of catheter lock solution, the use of prophylactic anticoagulation and monitoring of bone health. Strikingly, only two teams mentioned they monitored body composition, whereas our studies show that children with IF often have an abnormal body composition. Moreover, the frequency of micronutrient monitoring varied widely between the different European IF teams. For example, 25-OH vitamin D was measured with a frequency ranging from every 3 months to yearly, whereas some teams mentioned they never assessed micronutrients such as active vitamin B12, copper, chromium, selenium and manganese. Regarding the monitoring of bone health, most of the teams performed a yearly DEXA-scan, although 19% of the teams never used DEXA. In addition, the use of specific medication and monitoring of psychomotor development varied widely between teams. The variability of clinical practice among pediatric IF practitioners has also been shown in a recent survey among dietitians in the United States.[72]

Because of the complex care needed, it is essential that teams have enough experience to provide HPN care for children. The need for sufficient experience is an important argument for establishing regional referral centers in areas with multiple teams treating few patients. In 2018, the ESPGHAN/ESPEN/European Society for Paediatric Research published new guidelines about PN in children, including a chapter about HPN and one about complications.[73-75] It is stated that management of HPN by centralized units with expertise in the investigation of IF rehabilitation and with a multidisciplinary nutrition team to support care at home may minimize complications, improve outcome and allow weaning from PN as soon as possible.[74] An important addition in the new guideline[74] compared to the guideline from 2005[70] is the recommendation to measure body composition every 6-12 months.

Moreover, bone densitometry should be performed yearly and several micronutrients should be measured regularly, although the frequency of monitoring is not well defined.

METHODOLOGICAL CONSIDERATIONS

Study population

Since IF is a rare disease, one of the challenges in performing research in this group is the small sample size. To increase our sample size, we have been collaborating with the IF/HPN team in Amsterdam. Moreover, children with IF are a heterogeneous group. The populations described in this thesis were comparable to those in previous research, with short bowel syndrome as main cause of IF.[70,76-79] **Chapters 4 and 8** show higher percentages of patients with functional IF than in other chapters, because in the Netherlands most children with functional IF are treated in Amsterdam, which center participated in the multicenter studies described in these chapters. Next to the causes of IF, the percentage of children able to wean off PN was in agreement with that in previous studies.[19,20,80-85] The large diversity in age, diagnosis and duration of PN makes it difficult to draw a single conclusion on ways to optimize care for these patients. However, these clinical differences are inherent to IF, and reflect the current clinical practice.

Study design

Part of this thesis describes retrospective studies. Because of the limitations inherent to retrospective studies, we were not able to perform all the desired analyses, and collect detailed information. For example, relating detailed PN information with clinical outcomes such as growth and body composition was not possible. This is being investigated in an ongoing prospective study.

Next to this, patient selection bias may have occurred, since follow-up may be continued for patients not doing well, while others not experiencing any problems were not being followed anymore. Especially in the first years of the inclusion period of the retrospective studies, no strict protocol was followed. In addition, follow-up studies require active parent and patient participation, which may lead to over representation of patients and parents willing to participate in such studies.

Methods used

Another consideration is the use of air displacement plethysmography (BOD POD) for body composition measurement. Currently, there are no Dutch pediatric reference values available to compare our findings with. Therefore, we chose to compare it with reference data from the United Kingdom provided by experienced researchers in this field. Additionally, this method does not provide information on fat distribution (subcutaneous versus visceral fat), while this would be interesting to know, since visceral fat is a risk factor for cardio metabolic health more than overall fat.[86] Moreover, we did not perform a formal assessment of physical activity.

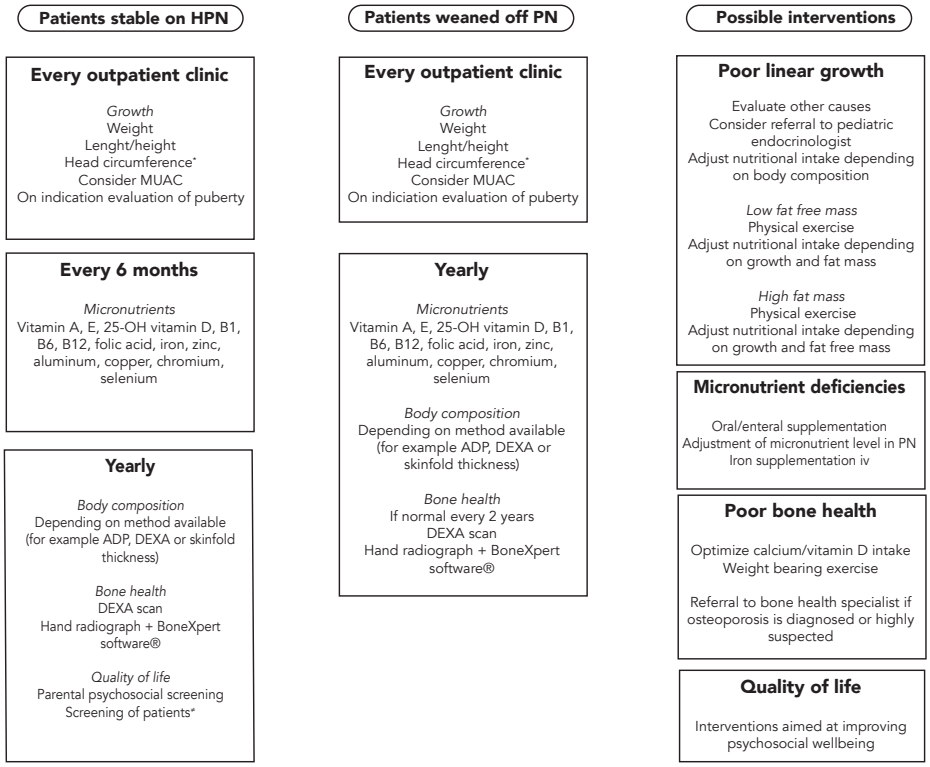
PROPOSAL FOR CLINICAL FOLLOW-UP

The results of our studies highlight the importance of close monitoring and follow-up of children with IF, both during and after weaning off PN. Continued monitoring after weaning off PN should preferably be performed by the multidisciplinary IF team, since this team already knows these children and has all the necessary team members available such as the dietitian. When this is not possible, follow-up could also be done by for example a pediatric gastroenterologist or general pediatrician, with close collaboration with a dietitian and pediatric surgeon when indicated. These healthcare professionals should be aware of the complications that occur due to IF and of the follow-up measurements that are required, such as a DEXA and micronutrient panel.

Previously, different guidelines on monitoring of possible complications have been suggested.[70,87] Our survey (**Chapter 11**) shows that bone health and micronutrient monitoring varies largely among European teams. In **Figure 2** we propose an algorithm for follow-up of growth, bone health and body composition based on the findings from our research and the current literature. Although important to have a standardized approach, it is also essential to tailor the follow-up and treatment to each individual patient. Moreover, IF teams are advised to focus not only on physical aspects, but also on developmental and social aspects of having IF. Based on our results we propose a yearly screening of parental psychosocial problems and QoL and psychosocial problems of patients, although the latter was outside the scope of this thesis. Currently, we are performing a study evaluating QoL, cognitive development and social-emotional functioning in children with IF.

Because of the improved survival, children with IF are now able to reach adulthood. The transfer of adolescent patients with IF to adult IF teams is therefore becoming increasingly important. Patients and their parents should actively participate in this process. A previous survey among British IF teams showed that currently the practices and processes of transition are highly variable.[88] A transition pathway and standards of care should be developed for adolescents on HPN transitioning into adult services. Having reached adolescent age, patients should learn how to handle the central venous catheter and administer the PN themselves. Also, those already weaned off PN should preferably be referred to adult services for continued follow-up, either gastroenterology, surgery or general practitioner practice, depending on the patient's condition and needs.

Figure 2. Algorithm for follow-up of patients with IF during and after weaning off PN



Legend: * Head circumference until 2 years of age. # Details about the evaluation of quality of life of patients with IF – i.e. what questionnaires and tests should be used – are currently lacking and should be determined based on future studies evaluating this topic.

Abbreviations: ADP, air displacement plethysmography; DEXA, dual energy X-ray absorptiometry; HPN, home parenteral nutrition; MUAC, mid upper arm circumference; PN, parenteral nutrition.

FUTURE RESEARCH

Optimal growth & body composition

The question remains, what nutrition and growth is optimal in children with IF, not only on the short term, but also on the long term. Should we aim for normal growth on 0 SD line, or should we accept that these children suffering from severe gastro-intestinal disease cannot achieve 'normal growth'? Should we aim for catch-up growth with PN, but to what extent of changed fat mass?

Clearly, monitoring of nutritional status should include body composition measurement. Preferably, this should be done from diagnosis onwards. Currently, we are performing a prospective observational study in children with IF from diagnosis onwards, including body composition measurement. Next to this measurement, it would be valuable to investigate functional tools as a marker for muscle function as well as a formal assessment of physical activity, for example using accelerometry.

Moreover, the effect of suboptimal growth on neurodevelopment, one of the major concerns resulting from inadequate growth, is currently unclear in these patients. In addition, impaired growth and body composition always need to be balanced against the benefits and risks of PN. These questions need to be addressed in future studies and emphasize the importance of establishing what optimal growth, body composition and nutrition is, including their effect on cardio-metabolic and neurodevelopmental outcome. Future studies should also evaluate the effects on body composition of interventions such as nutritional adjustments and physical activity exercise programs.

Next to growth and body composition, large prospective studies performed according to a strict protocol are necessary to give more insight in the actual prevalence of micronutrient deficiencies in relation to possible influencing factors.

Microbiota

Changes in the gut microbiota and its metabolic activity may be used as a marker of intestinal adaptation, in order to judge the optimal time and rate of transition from PN to enteral nutrition. Future studies should follow patients during the process of intestinal adaptation from the start of IF onwards. These studies should explore whether changes in the gut microbiota precede or follow intestinal adaptation. Currently, we are performing such a prospective study with the collection of fecal samples from the start of IF and onwards during the process of intestinal adaptation.

In our study, we were unable to relate changes in the gut microbiota to clinical outcomes such as liver disease and D-lactic acidosis, since none of our patients developed these

conditions. In order to evaluate associations of changes in the gut microbiota with these outcomes, larger multicenter trials are needed.

Next to a marker of intestinal adaptation, the altered gut microbiota may be a therapeutic target. The effect of more targeted antibiotics and the supplementation of pre-, pro- or synbiotics should be evaluated in future studies. Currently, there are no clear guidelines if fiber should be supplemented in patients with IF and if so, how much fiber should be used. Not only the response to fiber should be evaluated, but also the type (for example soluble versus non-soluble) and dose, especially since the microbial composition also influences the fermentation of fiber and therefore may lead to a different response in patients with IF.[57] Another possible therapeutic intervention might be fecal microbial transplantation, although so far only one case report in a child with D-lactic acidosis has been published.[89]

Effects of IF on development and attachment

Although it is well established that children with IF are exposed to multiple factors known to increase the risk of neurodevelopmental impairment, little is known about long-term neurodevelopmental outcomes of these children. Previous studies regarding neurodevelopmental outcomes had small sample sizes, used different methods and at different ages, which makes it difficult to interpret these results. These studies showed impaired psychomotor skills, varying from gross motor skills to visual-spatial skills.[60,90-95] Future studies should evaluate neurodevelopment, including identifying patients at high risk of developmental delays. It would be advisable to perform these evaluations in children who reach school age, when more subtle developmental delays or learning difficulties may become more apparent. The previous studies investigating psychomotor outcomes at school age were published in 2000 or before and neurodevelopmental outcomes may have improved, because of developments in treatment ever since that time. Moreover, these studies will provide an opportunity to explore possible interventions to improve and promote development.

Another important aspect to consider in future research is to get more insight in the quality of attachment between the child with IF and its parents. Secure attachment is thought to be the basis for future psychosocial competence, and is associated with better cognitive development later in life.[96,97] Several factors can be present that may impact early infant-parent attachment in IF, such as long hospitalization with multiple caregivers and changes in parental roles, hospital environment with invasive procedures and less opportunity for exploratory play and social interaction.[98] Moreover, the process of feeding and interaction between parents and child during feeding is important for good attachment, while this process is highly disturbed in children with IF because of the major feeding problems.[99,100] Also, after hospital admission, parents are trained to do all

the required complex medical treatments at home, including administration of the PN and emergency care of the central venous line. This demanding daily medical care can pressurize the parent's role in a child's development. Secure attachment is thought to be the basis for future psychosocial competence, and is associated with better cognitive development later in life.[96,97] It would therefore be of great value to include evaluation of child-parent attachment in future studies investigating psychosocial effects of IF.

General considerations

Since IF is a rare disease, future follow-up studies should preferably be multicenter. There are some good opportunities for collaboration through European Networks (ESPGHAN/ESPEN/European Reference Network Inherited and Congenital Anomalies of the intestinal tract), but more initiatives could be undertaken. A multicenter set-up requires standardization of data collection, availability of a good research infrastructure, satisfactory resources, the use of standardized definitions, and standardized outcome measures with the use of appropriate reference data.

CONCLUSION

The results from our studies show that IF is associated with high morbidity, not only the gastro-intestinal tract is affected. Moreover, our results emphasize the importance of close monitoring of bone health, growth, body composition and micronutrient deficiencies in children with IF, not only during PN but also after weaning off PN. In addition, healthcare professionals should be aware that parents of many children on HPN experience distress. All these problems support recommendation for multidisciplinary management of these children from diagnosis onwards and continuing after weaning of PN. With regard to organizational aspects, it appeared that treatment of IF is costly, and that a wide variation exists in organization and clinical practice of pediatric IF teams among Europe. Multicenter collaborations with standardized treatment and follow-up should be aimed for to further optimize care of children suffering from IF.

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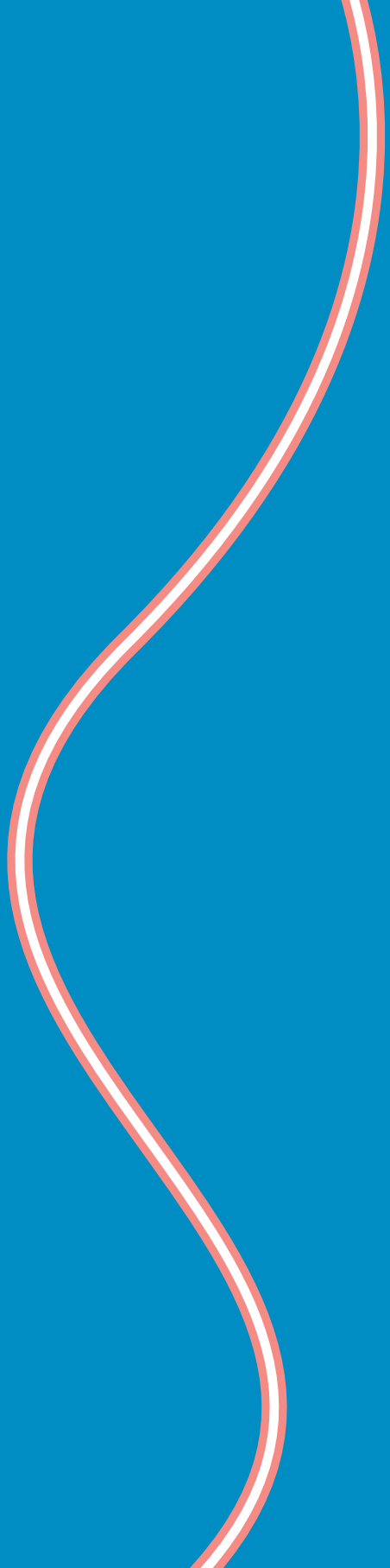

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Summary/samenvatting

SUMMARY

Intestinal failure (IF) occurs when the small intestine is too short or dysfunctional and cannot absorb enough nutrients and fluids. Since these nutrients and fluids are crucial for children to grow and develop, children with IF are dependent on nutrition directly administered intravenously, called parenteral nutrition (PN). This can be given at home as home PN (HPN). Over the last decades, the survival of patients with IF has improved tremendously, which has made the long-term outcomes and quality of life of patients with IF increasingly important. While complications such as line sepsis and liver failure are less common than before, long-term morbidities of IF such as poor bone health, abnormal body composition and psychosocial problems may arise. These are, however, currently not well explored. Additionally, information on organizational aspects including the current organization and clinical practice of pediatric IF teams, as well as the costs of care for children with IF is lacking. In this thesis we focus on outcomes of IF patients such as growth, body composition, bone health and the gut microbiome, as well as organizational aspects important in the care of these patients.

Chapter 1 provides the background and aims of the studies presented in this thesis. It contains a general introduction to IF and describes the gaps in current clinical practice and research.

PART 1 CLINICAL ASPECTS

The ultimate goal in the treatment of patients with IF, especially in those who had surgical resection, is to wean off PN i.e. gradually stop PN by promoting intestinal adaptation. This is the natural compensatory process that occurs after small bowel resection, and can be stimulated by giving enteral nutrition in gradually increasing amounts. In addition, medication can be used to either reduce factors that complicate this adaptation process or to stimulate intestinal adaptation. In **chapter 2** we describe the nutritional strategies and medication that best promote intestinal adaptation. Based on the literature, we concluded that to promote intestinal adaptation human milk or polymeric formula/feeding is recommended, depending on the age of the patient. Routinely used medication strategies to reduce complicating factors in the adaptation process are antisecretory and antidiarrheal medication, prokinetic drugs and antibiotics to treat small intestinal bacterial overgrowth. The glucagon like peptide-2 analogue teduglutide is suitable for adults with short bowel syndrome dependent on PN despite optimal medical therapy, but the effectiveness and safety in children should be further assessed before it can be used in clinical practice.

Chapter 3 describes the physical growth, body composition and prevalence of micronutrient abnormalities of 52 patients with IF receiving HPN during PN and after weaning. One year after the start of PN, children still dependent on PN were significantly shorter and lighter than the reference population. When already weaned off, children remained significantly lighter. Longitudinal evaluation showed catch-up growth during PN, but a significant decrease of height after weaning off PN. Weight did not change significantly after weaning, suggesting that patients weaned off PN may suffer from chronic malabsorption and receive enough nutrition for maintaining their weight, but not their linear height course. When evaluating body composition measured with dual energy X-ray absorptiometry (DEXA), children with IF had significant lower fat free mass. In addition, we found frequent micronutrient deficiencies, including vitamin A, E, 25-OH vitamin D, zinc and iron. These micronutrient deficiencies were not only found during PN, but also after weaning off. These results emphasize the importance of monitoring growth, body composition and micronutrients, which should also be continued after achieving intestinal autonomy.

In **chapter 4** we describe a prospective two-center cohort study in which we assessed growth and body composition in 22 children with IF receiving long-term PN. To evaluate body composition, we used air displacement plethysmography. We found again that children with IF were significantly lighter and shorter than the normal population mean. Moreover, they had significant higher fat mass and lower fat free mass than healthy references. Weight-for-height and body mass index (BMI) were significantly associated with fat free mass, and BMI with fat mass. However, weight-for-height and BMI were not significantly different than the normal population mean and children with the same weight and height showed different body composition. In 13 patients with a follow-up measurement after 1 year, growth and body composition did not change significantly. We concluded that despite close monitoring of growth and adjustment of nutritional requirements, children with IF have abnormal body composition. Indices based on weight and height alone are not sufficient and body composition should be measured to be informed about the fat mass and fat free mass. The question remains what optimal growth is. Future research needs to evaluate the effect of a patient-tailored approach including nutritional adjustments and physical activity advice based on growth and body composition instead of growth measurements only.

Chapter 5 describes the results of a retrospective study in which the bone health of children with IF was evaluated. In addition, two methods to assess bone health were compared: DEXA and digital X-ray radiogrammetry using special software, called BoneXpert. In a population of 46 children who underwent a DEXA measurement or hand radiograph, 24% of the children had a low bone mineral density at the first DEXA. When we corrected for growth failure, this percentage was reduced to 16%. At the first hand

radiograph 50% of the children had poor bone health. This higher number as compared to the percentage based on DEXA, might be caused by the fact that hand radiographs were performed in younger children who were considered to have a higher risk of low bone mineral density. We found that children with IF have a significantly poorer bone health than the reference population, also after weaning off PN. Age, duration of PN and surgical IF were associated with lower bone health at the first DEXA scan. When comparing the DEXA scans and hand radiographs, these methods showed good agreement, especially for Z-scores below -2 which are considered abnormal. Therefore, using hand radiographs with the BoneXpert software seems to be a feasible method for monitoring bone health in children with IF, although this needs to be confirmed in a larger prospective study. In our IF population of the last 13 years, 3 patients developed bone fractures and received bisphosphonate treatment. The addendum of chapter 5 describes these patients in detail and shows that after the start of bisphosphonates two patients did not develop new fractures.

Chapter 6 reviews what is known about the gut microbiome in adult and pediatric patients with IF based on previously published studies. Following this literature review, we concluded that patients with IF have an altered gut microbiome. Overall bacterial diversity is remarkably decreased. Profound shifts are described from a microbiome dominated by Firmicutes to dominance by Proteobacteria, especially Enterobacteriaceae. In addition, overabundance of Lactobacillus is commonly found. One study evaluating the metabolic activity of the gut microbiome showed that children with IF had a lower concentration of acetate, but similar concentrations of butyrate, propionate and total short-chain fatty acids. Gut microbiome characteristics have been associated with poor growth, liver disease, D-lactic acidosis and duration of intestinal adaptation. Future research should explore the value of changes in the gut microbiome and its metabolic activity as a biomarker to judge the optimal time of transition from PN to enteral nutrition. Next to this, there is potential to use the gut microbiome as a modifiable therapeutic target to optimize outcomes of patients with IF.

As a first step to unravel associations between the microbiome, its metabolites and gut adaptation, we prospectively analyzed the microbiota and its metabolic activity of 15 children receiving long-term PN (**chapter 7**). Sixty-eight serial samples were collected during two years and compared to 25 single control samples from healthy children. We found that patients with IF had lower levels of butyrate, propionate and total short-chain fatty acids, and higher levels of D and L lactate than healthy controls. In addition, patients with IF had lower bacterial diversity and richness, presumptive markers of optimal gut health. Loss of dominant microbial taxa and increased abundance of sub-dominant and potential harmful species was seen. IF patients had an increased relative abundance of Proteobacteria, normally representing a very small fraction of the gut microbiota and

including many opportunistic pathogens. On the other hand, the relative abundance of Bacteroidetes and Firmicutes, known as main fiber fermenters and short-chain fatty acids producers, was decreased. Patients with surgical IF had lower bacterial diversity than functional IF patients.

When evaluating associations between the gut microbiota and clinical variables, we found that the percentage of calories provided by PN, a marker of PN dependency, was negatively associated with microbial diversity. Duration of PN, the percentage of calories provided by PN and fiber intake explained most of the variation in microbial community structure. Two patients weaned off PN; after weaning their microbial structure moved closer to that of the healthy controls. Future research should explore whether these changes precede or follow intestinal adaptation, as well as the association between dysbiosis features and clinical outcomes.

Next to medical consequences, having IF can have profound psychosocial consequences for both patients and their families. **Chapter 8** focuses on the quality of life of parents with children on HPN, analyzed among 37 mothers and 25 fathers of 37 children on HPN in two centers. In general, parents of children with IF reported the same health-related quality of life as the reference group, except that mothers of children on HPN reported higher levels of depression compared to the reference group. Moreover, both parents reported higher levels of distress and everyday problems. Structural screening for parental psychosocial problems is essential in clinical practice to improve the well-being of these parents and their children.

PART II ORGANIZATIONAL ASPECTS

Exact data on Dutch patients with chronic IF and patients after intestinal transplantation have been lacking. In **chapter 9** the results of a multicenter registry of adult and pediatric patients with IF in the Netherlands are described. In total, 195 patients (158 adults, 37 children) with chronic IF were identified, leading to a Dutch point prevalence of chronic IF of 11.62 per million on January 1, 2013. Fifty-seven patients had one or more indications for intestinal transplantation, whereas 12 patients actually underwent intestinal transplantation since its introduction in the Netherlands. As shown in this study, multicenter registries are able to facilitate the monitoring of individual patients, thereby supporting multidisciplinary care and decision-making and comparison of practices between centers.

Chapter 10 reports the costs of treatment of children with IF, and evaluates the cost-effectiveness of intestinal rehabilitation (IR) by using a discrete-event model. Intestinal rehabilitation consists of a systematic approach to stimulate intestinal adaptation and includes optimizing parenteral, enteral and oral feeding, while maintaining growth, preventing complications and maintaining a good quality of life. We evaluated the cost-effectiveness of IR by comparing two scenarios: one with IR, and one without IR. In the scenario with IR, a proportion of patients representing those with the ability to wean off PN underwent IR, whereas the remaining patients directly progressed to HPN without undergoing IR. In the scenario without IR, all patients progressed to HPN without undergoing IR. In both scenarios, a proportion of patients on HPN was eventually eligible for intestinal transplantation. IR prolonged survival, and was associated with cost savings. Costs mainly included hospital admissions and PN. Based on our simulations, we considered intestinal rehabilitation to be a cost-effective treatment for children with IF.

Chapter 11 highlights the organization and clinical practice of IF teams across Europe using an online survey. Sixty-one IF teams representing 20 countries completed the first general part of the survey, whereas 59 teams completed the second part with more detailed questions. We concluded that there is a wide diversity of the composition of IF teams with regards to type of health care providers/staff and the number of patients treated by a team, which ranged from 1-125. Overall, there was a good compliance to the existing European guideline at that time (published in 2005). Clinical practice that varied the most was the standard use of medication, such as probiotics, somatostatin analogues and the use of prophylactic anticoagulation. In addition, standard monitoring of long-term complications such as bone health varied widely. In order to optimize care of children with IF, experience regarding specific treatment options should be shared, and international agreement on standards of care is needed, including implementation of the guideline.

The last section of this thesis (**chapter 12**) compromises an overview of the most important findings, together with a discussion of their clinical implications, methodological considerations and recommendations for future research and clinical practice.

SAMENVATTING

Darmfalen wordt gekenmerkt door onvoldoende opname van voedingsstoffen en vocht door de dunne darm. Dit wordt veroorzaakt doordat er onvoldoende darmoppervlak is, bijvoorbeeld doordat een deel van de dunne darm chirurgisch is verwijderd, of doordat de darm niet goed genoeg functioneert. Om er voor te zorgen dat kinderen met darmfalen kunnen groeien, zijn zij afhankelijk van parenterale voeding (TPV), waarbij voedingstoffen direct in de bloedbaan worden toegediend. TPV kan in de thuissituatie gegeven worden, in dit proefschrift wordt hiernaar verwezen als TPV thuis. De prognose van darmfalen bij kinderen is de laatste 15 jaar sterk verbeterd. Door deze verbeterde overleving worden lange termijn uitkomsten en kwaliteit van leven steeds belangrijker. TPV is nog steeds geassocieerd met frequent voorkomende en potentieel levensbedreigende complicaties. Echter, over veel van deze lange termijn effecten is op dit moment onvoldoende bekend. Daarnaast is er weinig bekend over de organisatie van de zorg, het huidige beleid van de zogenaamde darmfalenteams en de bijbehorende kosten van deze zorg. Dit proefschrift beschrijft de uitkomsten van kinderen met darmfalen en gaat voornamelijk in op de groei, lichaamssamenstelling, botdichtheid en het microbioom van de darm (verzameling van micro-organismen). Daarnaast worden organisatorische aspecten beschreven die belangrijk zijn bij de zorg voor kinderen met darmfalen.

In **hoofdstuk 1** introduceren wij de onderwerpen die in de hierop volgende hoofdstukken worden besproken. Eerst lichten wij toe wat darmfalen is en welke complicaties met darmfalen en TPV gepaard gaan. We schetsen de bestaande hiaten in de huidige klinische praktijk en wetenschap.

DEEL 1 KLINISCHE ASPECTEN

Het belangrijkste doel bij het behandelen van patiënten met darmfalen, vooral wanneer een deel van de dunne darm chirurgisch is verwijderd, is ervoor zorgen dat er geen noodzaak meer is tot het geven van TPV. Dit wordt gedaan door het stimuleren van adaptatie van de darm. Adaptatie is het proces waarbij er een grotere opnamecapaciteit ontstaat. Dit kan tot jaren na een grote dunne darm resectie optreden. In **hoofdstuk 2** wordt besproken welke processen plaatsvinden tijdens adaptatie van de darm en hoe dit het beste kan worden beïnvloed door voeding en specifieke medicatie. Op basis van de literatuur concludeerden wij dat om adaptatie te bevorderen het beste moedermelk of polymere voeding gegeven kan worden, afhankelijk van de leeftijd van de patiënt. Veel gebruikte medicatie om complicaties in het adaptatieproces te verminderen zijn anti-secretoire middelen, middelen tegen diarree, prokinetica en antibiotica voor de behandeling van bacteriële overgroei. Het medicijn Teduglutide, een analoog van het

glucagonachtige peptide-2, is geschikt voor de behandeling van volwassenen met het kortedarmsyndroom, ontstaan na verwijdering van een groot deel van de dunne darm, die ondanks optimale behandeling afhankelijk zijn van TPV. De effectiviteit en veiligheid van dit medicijn bij kinderen moet verder onderzocht worden voordat het in de dagelijkse klinische praktijk gebruikt kan worden.

In een retrospectieve studie (**hoofdstuk 3**) keken wij naar de groei, lichaamssamenstelling en micronutriënten (vitamines, mineralen en sporenelementen) van 52 kinderen met darmfalen tijdens en na behandeling met TPV thuis. Eén jaar na de start van TPV waren de patiënten afhankelijk van TPV kleiner en lichter dan de referentie populatie. Ook wanneer de patiënten geen TPV meer kregen, bleven ze lichter. Longitudinale analyses lieten inhaalgroei zien tijdens TPV, maar een significante afname van de lengte na het stoppen van TPV. Het gewicht veranderde niet significant na het stoppen van de TPV. Het zou kunnen dat patiënten na het stoppen van de TPV lijden aan chronische malabsorptie, waarbij ze nog voldoende voeding krijgen om hun gewicht op peil te houden, maar niet hun lengte groei. Met behulp van DEXA scans keken wij naar de lichaamssamenstelling, waarbij patiënten met darmfalen significant minder vetvrije massa hadden. Daarnaast zagen we geregeld micronutriënt tekorten, met name voor vitamine A, E, D, zink en ijzer. Deze tekorten werden niet alleen gevonden tijdens, maar ook na de behandeling met TPV. Deze resultaten tonen aan dat het belangrijk is om groei, lichaamssamenstelling en micronutriënten goed te monitoren, niet alleen tijdens de behandeling met TPV, maar ook daarna. Het is dus van belang deze kinderen poliklinisch te blijven volgen, ook na het staken van de TPV.

In **hoofdstuk 4** beschrijven wij een prospectieve observationele studie, waarin wij de groei en lichaamssamenstelling onderzochten bij 22 patiënten met darmfalen in twee centra. Voor het meten van de lichaamssamenstelling maakten wij gebruik van 'air displacement plethysmography', waarbij er gebruik gemaakt wordt van luchtverplaatsing. Wij zagen dat deze patiënten meer vet hadden en minder vetvrije massa hadden dan gezonde kinderen. Gewicht-voor-lengte en body mass index (BMI) waren significant geassocieerd met vetvrije massa, en BMI met vetmassa. Echter, gewicht-voor-lengte en BMI waren niet verschillend van gezonde kinderen en patiënten met dezelfde BMI of gewicht-voor-lengte hadden een verschillende lichaamssamenstelling. Bij 13 patiënten werd er een 2e meting verricht na 1 jaar, waarbij we geen veranderingen zagen in groei of lichaamssamenstelling. We concludeerden dat ondanks intensieve monitoring van groei en aanpassing van de voeding, kinderen met darmfalen abnormale groei en lichaamssamenstelling hebben. In de praktijk moet er niet alleen gekeken worden naar de gebruikelijke parameters gewicht en lengte, maar zou de lichaamssamenstelling gemeten moeten worden voor evaluatie van de vetmassa en vetvrije massa. De vraag blijft wat optimale groei is voor deze kinderen. Toekomstig onderzoek dient het effect

van een op de patiënt afgestemde behandeling te evalueren, welke dient te bestaan uit aanpassingen van de voeding, maar ook advies met betrekking tot fysieke activiteit, gebaseerd op meting van groei en lichaamssamenstelling.

Naast groei en lichaamssamenstelling, hebben wij gekeken naar de botdichtheid van patiënten met darmfalen (**hoofdstuk 5**). In deze studie werden twee methoden voor het monitoren van de botdichtheid vergeleken: de DEXA scan en de röntgenfoto van de hand bewerkt met speciale software, BoneXpert genoemd. In een groep van 46 kinderen die één van deze twee onderzoeken hadden ondergaan, constateerden we dat 24% van hen een lage botdichtheid had bij de eerste DEXA scan. Wanneer we corrigeerden voor hun achterblijvende groei, daalde dit percentage naar 16%. Bij de eerste handfoto had 50% een lage botdichtheid. Dit hogere percentage ten opzichte van het percentage gevonden bij de DEXA scan kan mogelijk verklaard worden door het feit dat de handfoto's gemaakt werden bij jongere kinderen met een hogere kans op een lage botdichtheid. Kinderen met darmfalen hadden een significant lagere botdichtheid dan de referentie populatie, ook na het stoppen van de TPV. Leeftijd, duur van de TPV en het hebben van chirurgisch darmfalen waren geassocieerd met een lagere botdichtheid bij de 1e DEXA scan. De botdichtheid op basis van de DEXA scan en handfoto kwamen goed overeen, met name in het geval van Z-scores onder de -2, welke als abnormaal worden beschouwd. De handfoto met BoneXpert software lijkt een bruikbare methode in de klinische praktijk voor het beoordelen van botgezondheid, hoewel dit nog in een grotere onderzoeksgroep bevestigd zal moeten worden. Van de groep kinderen met darmfalen die de in de afgelopen 13 jaar bij ons onder behandeling waren, hadden 3 patiënten meerdere fracturen waarvoor zij met bisfosfonaten behandeld werden. Twee van hen ontwikkelden na de start van de bisfosfonaten geen nieuwe fracturen meer. Het addendum van hoofdstuk 5 omvat een gedetailleerde beschrijving van deze patiënten.

In **hoofdstuk 6** beschrijven wij door middel van een literatuurstudie wat er bekend is over het darm microbioom bij patiënten met darmfalen, zowel volwassenen als kinderen. Op basis van de huidige literatuur concludeerden wij dat patiënten met darmfalen een ander microbioom hebben dan gezonde mensen. Het microbioom van patiënten met darmfalen blijkt veel minder divers. Daarnaast is er een verschuiving van een microbioom met veel Firmicutes naar een microbioom met veel Proteobacteria en met name Enterobacteriaceae. Hiernaast worden er veel Lactobacillus bacteriën gezien. Wat betreft de metabole activiteit van het microbioom werd er in één studie beschreven dat kinderen met darmfalen lagere concentraties acetaat hebben, maar dezelfde hoeveelheden butyraat, propionaat en totale korte-keten vetzuren als gezonde controles. Bepaalde veranderingen in het microbioom worden in de literatuur geassocieerd met slechte groei, leverfalen, D-lactaat acidose en duur van adaptatie van de darm. In toekomstig onderzoek zou er gekeken moeten worden of veranderingen in het microbioom en de

metabole activiteit van het microbioom als marker gebruikt kunnen worden tijdens het adaptatieproces van de darm, om zo het optimale moment van transitie van TPV naar enterale voeding te beoordelen. Daarnaast kan het microbioom een aangrijpingspunt zijn voor diverse behandelingen bij patiënten met darmfalen.

Als eerste stap in dit proces hebben wij het microbioom en de metabole activiteit prospectief geanalyseerd bij 15 kinderen met darmfalen die langdurig afhankelijk waren van TPV (**hoofdstuk 7**). Hiervoor verzamelden wij 68 samples gedurende 2 jaar en vergeleken deze met samples van 25 gezonde controles. We vonden dat patiënten met darmfalen lagere hoeveelheden butyraat, propionaat en totale korte-keten vetzuren hadden, en hogere hoeveelheden D en L lactaat dan gezonde controles. Daarnaast had het microbioom van patiënten met darmfalen een lagere diversiteit en rijkheid, welke worden gezien als weerspiegeling van de (on)gezondheid van de darm. Tevens werd een toename van potentieel schadelijke bacteriën gezien en een afname van bacteriën die als gunstig worden beschouwd. Darmfalen patiënten hadden een verhoogde relatieve hoeveelheid Proteobacteria, welke normaal gesproken maar een klein deel vormen van het microbioom en daarnaast bestaan uit meerdere opportunistische pathogenen. De relatieve hoeveelheid Bacteoridetes en Firmicutes, belangrijk voor het fermenteren van vezels en produceren van korte-keten vetzuren, was verlaagd. Patiënten met chirurgisch darmfalen hadden een minder divers microbioom dan patiënten met functioneel darmfalen.

Hoe hoger het percentage van calorieën middels TPV was, vaak gebruikt als marker van TPV afhankelijkheid, hoe minder divers het microbioom was. De duur van TPV, het percentage van de totale calorieën die middels TPV gegeven werden en de vezelintake waren de belangrijkste klinische factoren die verschillen in het microbioom verklaarden. Gedurende de studie konden 2 van de 15 patiënten stoppen met TPV. Hoe langer zij gestopt waren met TPV, hoe meer hun microbioom leek op dat van de gezonde controles. Toekomstig onderzoek moet uitwijzen of deze veranderingen voorafgaan of volgen op adaptatie van de darm, en dient zich te focussen op de relatie tussen veranderingen in het microbioom en klinische uitkomstmaten.

Naast medische uitkomsten, evalueerden wij ook psychosociale uitkomsten van ouders van kinderen met darmfalen. We vonden dat ouders van kinderen met TPV thuis globaal gezien dezelfde kwaliteit van leven rapporteerden als ouders van gezonde kinderen (**hoofdstuk 8**). Echter, moeders van kinderen met TPV thuis rapporteerden een hogere mate van depressieve klachten en beide ouders rapporteerden een hogere mate van stress en dagelijkse problemen. Om het welzijn van kinderen met darmfalen en hun ouders te verbeteren is structurele screening voor psychosociale problemen van essentieel belang.

DEEL II ORGANISATORISCHE ASPECTEN

Precieze data over Nederlandse patiënten met darmfalen en patiënten na dunne darmtransplantatie ontbraken lange tijd. In **hoofdstuk 9** worden de resultaten beschreven van een multicenter registratie van Nederlandse patiënten met darmfalen, zowel volwassenen als kinderen, die bekend waren op 1 januari 2013. In totaal werden er 195 patiënten geïdentificeerd, waarvan 158 volwassenen en 37 kinderen, wat leidde tot een punt prevalentie van chronisch darmfalen van 11,62 per miljoen op 1 januari 2013. Van deze 195 patiënten voldeden 57 patiënten aan één of meerdere indicaties voor dunne darmtransplantatie, terwijl er 12 patiënten daadwerkelijk een transplantatie ondergingen. Deze multicenter registratie kan het monitoren van individuele patiënten faciliteren.

Hoofdstuk 10 beschrijft de kosten van de behandeling van kinderen met darmfalen en de kosteneffectiviteit van darm revalidatie. Darmrevalidatie bestaat uit een systematische aanpak om intestinale adaptatie te stimuleren, waaronder het optimaliseren van TPV, enterale en orale voeding, het zorgen voor groei en voorkomen van complicaties. De kosteneffectiviteit werd geëvalueerd met behulp van een 'discrete-event model'. We vergeleken hierbij twee scenario's: één met darmrevalidatie en één zonder. In het tweede scenario gingen alle patiënten over op TPV thuis zonder eerst eventuele darmrevalidatie te ondergaan. In beide scenario's konden patiënten uiteindelijk een dunnedarmtransplantatie ondergaan. Uit dit model bleek dat darmrevalidatie zorgt voor een betere overleving en kostenbesparing. Darmrevalidatie wordt dus beschouwd als een kosteneffectieve behandeling. De voornaamste kosten van de behandeling bestonden uit ziekenhuisopnames en TPV.

In **hoofdstuk 11** beschrijven wij de organisatie en klinische praktijk van darmfalenteams in Europa, welke onderzocht is met behulp van een vragenlijst. Eenenzestig darmfalenteams uit 20 landen vulden het eerste algemene deel van deze vragenlijst in en 59 teams de volledige vragenlijst, die meer specifieke vragen omvatte. Wij concludeerden dat er sprake is van een grote diversiteit tussen de samenstelling van de verschillende darmfalenteams, zowel in aantal en soort professionals, als in aantallen patiënten die behandeld werden door deze teams, variërend van 1 tot 125. In het algemeen hielden de meeste teams zich goed aan de op dat moment beschikbare richtlijn (gepubliceerd in 2005). De klinische praktijk verschilde het meest van de richtlijn wanneer gekeken werd naar welke medicatie standaard gebruikt werd, waaronder probiotica, somatostatine analogen en het gebruik van profylactische antistolling. Daarnaast was er een grote variatie in de wijze waarop en frequentie waarmee de botdichtheid van kinderen met darmfalen werd gemonitord. Om de zorg voor kinderen met darmfalen te kunnen verbeteren, is het cruciaal om ervaringen met betrekking tot specifieke behandelingen te

delen en is het belangrijk om op nationaal en internationaal niveau afspraken te maken over de behandeling, inclusief het volgen en implementeren van de richtlijn.

In de algemene discussie (**hoofdstuk 12**) wordt een overzicht gegeven van de belangrijkste bevindingen uit het proefschrift in verhouding tot de bevindingen uit eerder beschreven onderzoeken. De betekenis van deze bevindingen voor de behandeling van patiënten met darmfalen wordt bediscussieerd en er worden aanbevelingen gedaan voor verder onderzoek en de klinische praktijk.

PART IV

APPENDICES

ABBREVIATIONS

%FM	percentage fat mass
ADP	air displacement plethysmography
BC	body composition
BHI	bone health index
BMAD	bone mineral apparent density
BMD	bone mineral density
BMI	body mass index
BSPGHAN	British Society of Paediatric Gastroenterology, Hepatology and Nutrition
CI	confidence interval
CIF	chronic and/or irreversible intestinal failure
CIPO	chronic intestinal pseudo-obstruction
CRBSI	catheter-related bloodstream infection
CVC	central venous catheter
DEXA/DXA	dual energy x-ray absorptiometry
DRIFT	Dutch Registry of Intestinal Failure and Intestinal Transplantation
DXR	digital x-ray absorptiometry
EN	enteral nutrition
ESPEN	European Society for Clinical Nutrition and Metabolism
ESPGHAN	European Society for Paediatric Gastroenterology, Hepatology and Nutrition
FFM	fat free mass
FM	fat mass
GH	growth hormone
GLP-1	glucagon-like peptide-1
GLP-2	glucagon-like peptide-2
GOR	grade of recommendations
HFA	height-for-age
HGF	hepatocyte growth factor
HPN	home parenteral nutrition
ICER	incremental cost-effectiveness ratio
IGF	insulin-like growth factor
IF	intestinal failure
IQR	interquartile range
IR	intestinal rehabilitation
ITx	intestinal transplantation
LCP	long-chain polyunsaturated fatty acids
LCT	long-chain triglycerides

LMWH	low molecular weight heparin
LOE	levels of evidence
LS	lumbar spine
MCT	medium-chain triglycerides
NA	not applicable
PICC	peripheral inserted central catheter
PN	parenteral nutrition
PPIs	proton pump inhibitors
SBS	short bowel syndrome
SCFAs	short-chain fatty acids
SD(S)	standard deviation (score)
SIBO	small intestinal bacterial overgrowth
TB	total body
TH	target height
QoL	quality of life
WFA	weight-for-age
WFH	weight-for-height

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PhD PORTFOLIO

Erasmus MC Department Paediatric Gastroenterology
PhD period March 2014 – March 2018
Promotors Prof. dr. E.H.H.M. Rings and prof. dr. R.M.H. Wijnen
Co-promotor Dr. J.M. Hulst

PhD training	Year	ECTS
General courses		
Research Integrity (Erasmus MC)	2015	0.3
Biomedical English Writing and Communication (Erasmus MC)	2015	3.0
BROK ('Basiscursus Regelgeving Klinisch Onderzoek', NFU BROK academy)	2014	1.0
Biostatistical Methods 1: Basic Principles (NIHES)	2014	5.7
Specific courses		
Young Investigators Forum (European Society for Paediatric Gastroenterology, Hepatology and Nutrition)	2016	1.0
Photoshop and Illustrator (Molmed)	2016	0.3
Summer Course (Research Master Infection & Immunity)	2015	7.2
Summer school on Paediatric Nutrition (European Society for Paediatric Gastroenterology, Hepatology and Nutrition)	2015	2.0
Cohort studies (NIHES)	2014	0.7
Presentations at conferences		
European Society for Paediatric Gastroenterology, Hepatology and Nutrition (oral)	2019	1.0
European Society for Paediatric Gastroenterology, Hepatology and Nutrition (oral)	2018	1.0
Digestive Disease Days (oral)	2018	1.0
International Congress of the Intestinal Rehabilitation and Transplant Association (oral + poster presentation (2x))	2017	1.0
Digestive Disease Week (poster presentation)	2017	1.0
Network for Intestinal Failure and Transplantation in Europe (oral)	2016	1.0
Pediatric Intestinal Failure Symposium (poster presentation (3x))	2016	1.0
European Society for Paediatric Gastroenterology, Hepatology and Nutrition (poster presentation (3x))	2016	1.0
International Small Bowel Transplant Symposium (oral + poster presentation)	2015	1.0
International Small Bowel Transplant Symposium (poster presentation)	2013	1.0
Nederlandse Vereniging voor Gastroenterologie (oral)	2013	1.0
Local research meetings		
Research meeting Pediatric Surgery	2016-2018	0.5
Research meeting Metabolism, Endocrinology and Nutrition	2014-2018	0.5
Research meeting Pediatric Gastroenterology and laboratory of Pediatric Gastroenterology	2014-2018	0.5
Annual Sophia Research Day	2014-2018	0.5

Teaching		
Lecturing		
Lecture 'Intestinal Failure' for nurses, hospital pharmacists, other medical professionals	2015-2017	1.0
Supervising Master's theses		
B. van Schijndel, student nutrition and dietetics, Hogeschool Arnhem en Nijmegen	2016-2017	2.0
L. Strengers, medical student. Erasmus University	2016	2.0
N. Rijnen, medical student, Erasmus University	2015	2.0
Other		
Supervision Minor project TU Delft	2015	1.0
Other		
Participation in TULIPS PhD program	2016-2018	0.5
Board member Sophia Researchers Association	2016-2017	1.0
Peer review of articles for international scientific journals	2014-2018	0.5

ABOUT THE AUTHOR

Esther Neelis was born on the 23rd of November 1988 in Heerenveen, the Netherlands.

She completed her high school at the Bornego College Heerenveen in 2007. In the same year she started her medical training at the University of Groningen. Her enthusiasm for research and intestinal failure started in 2013 when she performed a research project at the Department of Pediatric Gastroenterology and the Department of Gastroenterology at the University Medical Center Groningen, under supervision of prof. dr. E. Rings and prof. dr. G. Dijkstra. Esther graduated in November 2013, after which she spent some time travelling.

In March 2014 she started with her PhD project focusing on optimizing care for children with intestinal failure at the Department of Pediatric Gastroenterology and Pediatric Surgery at the Erasmus MC-Sophia Children's Hospital, under guidance of prof. dr. E. Rings, prof. dr. R. Wijnen, and dr. J. Hulst). During this period she was a board member of the Sophia Researchers Association and organized the Theme Sophia Research Days in 2016 and 2017. In addition, she followed the Training Upcoming Leaders in Paediatric Science PhD Curriculum. In April 2018 Esther started as a pediatric resident (ANIOS) at the Maasstad Ziekenhuis, Rotterdam. From January 2019 onwards she continued working at the Maasstad Ziekenhuis as a pediatric resident (AIOS). She is looking forward to combine clinical work with science in her future career.

Waar ik mij goed voel ben ik thuis

Erasmus

DANKWOORD

Eten is iets wat we vaak als vanzelfsprekend ervaren. Waar ik de afgelopen jaren menig avond in een restaurant of café heb doorgebracht, is dat voor patiënten met darmfalen niet zo vanzelfsprekend. De impact hiervan is iets wat ik me voor het doen van dit onderzoek nooit zo had gerealiseerd. Allereerst wil ik daarom alle kinderen en ouders die hebben meegedaan aan één of meerdere onderzoeken bedanken. Jullie waren bereid om in te stemmen met deelname aan wetenschappelijk onderzoek in een vaak zeer moeilijke periode. De afgelopen jaren heb ik veel geleerd over onderzoek doen, maar nog meer van jullie! Mijn bewondering voor jullie veerkracht is groot. Jullie zijn de belangrijkste drijfveer geweest achter dit onderzoek, en ik hoop dan ook met mijn onderzoek te hebben bijgedragen aan het verbeteren van de zorg voor patiënten met darmfalen. Dankzij jullie heb ik altijd met veel plezier het onderzoek uitgevoerd en was iedere poli weer een feest!

Een proefschrift schrijven doe en kun je niet alleen. Ik heb de afgelopen jaren met veel mensen mogen samenwerken. Op deze plek wil ik iedereen die heeft bijgedragen aan het tot stand komen van mijn proefschrift heel erg bedanken. Een aantal van hen wil ik in het bijzonder noemen.

Mijn promotoren: prof. dr. E. Rings en prof. dr. R. Wijnen. Beste Edmond, wie had kunnen denken dat een onderzoeksproject in Groningen uiteindelijk zou leiden tot deze promotie? Ik 6 jaar geleden niet! Ik kan me het moment nog goed herinneren dat jij na een congres in Cambridge in de pub vroeg of ik geïnteresseerd zou zijn in een PhD. Zonder onze samenwerking destijds was ik nooit bij deze promotie én in Rotterdam terechtgekomen. Ik wil je bedanken voor deze unieke kans! Bedankt ook voor de mogelijkheden die je me hebt gegeven om congressen en cursussen over de gehele wereld te kunnen bijwonen! Ik bewonder je rust en het feit dat je ondanks je 2 banen altijd tijd voor mij had. Dank voor al je interesse en vertrouwen. Op naar nieuwe projecten!

Beste René, al snel waren we er over uit: we hebben een kinderchirurg nodig in ons onderzoeksteam. Dank voor je vertrouwen en enthousiasme op de momenten dat ik het zelf soms even niet zag zitten. Ook over de onderwerpen die niet direct chirurgisch waren, was je minstens net zo enthousiast. Ook jou wil ik bedanken voor de mogelijkheden die je mij hebt gegeven om op diverse congressen ons werk te presenteren.

Mijn copromotor, dr. J. Hulst. Lieve Jessie, ik had me geen betere copromotor kunnen wensen. Je bent voor mij een groot voorbeeld hoe je kliniek, onderzoek en privé kunt combineren. Je stond (en staat) altijd klaar om mij van advies te voorzien. Zonder jou was dit promotietraject zeker niet zo'n succes geworden. Altijd wist je mij verder te helpen met opbouwende feedback en je statistische kennis. Al was het laatste jaar meer op

afstand, ik kon altijd met vragen bij je terecht. Ik hoop dan ook dat we in de toekomst nog veel mogen samen werken, wie weet in Toronto?

Dr. B. de Koning, lieve Barbara, officieel geen tweede copromotor, maar zo voelde het vaak genoeg wel – zeker in het laatste stuk van mijn promotie. Zonder jou waren de microbioom artikelen er niet geweest. Dank voor al je hulp, begeleiding en gezellige koffie momenten. Je enthousiasme en kritische blik (op zoek naar de flow ;-)) heeft het onderzoek iedere keer weer verder gebracht. Op naar nog meer mooie samenwerkingen de komende jaren!

De commissieleden: prof. dr. J. Escher, beste Hankje, dank voor het vervullen van de rol van secretaris binnen de kleine commissie. Dank voor de interesse die je altijd had in het darmfalen onderzoek, iets waar jij vele jaren geleden grondlegger van bent geweest. Prof. D. Tibboel, ik ben vereerd dat u als grondlegger van het darmfalenteam zitting wilt nemen in mijn commissie. Dr. M. Tabbers, beste Merit, dank voor de fijne samenwerking de afgelopen jaren en het plaatsnemen in de commissie.

Prof. dr. G. Dijkstra, beste Gerard, ooit begonnen als student in Groningen, ben ik dan ook vereerd dat u in de grote commissie wilde plaatsnemen, dank daarvoor. Prof. dr. P. Wales, thank you for your willingness to be a member of the committee. Dr. K. Gerasimidis, dear Kostas, I am grateful and honored that you are part of the committee, thank you for all your help the past years. Thank you for introducing me to the microbiome world and all the energetic skype meetings we had. I am looking forward to future collaborations!

Wat was het fijn om als onderzoeker deel te mogen uit maken van het darmfalenteam. Conny, Hester, Marjolein, Joanne, Wendy, Jolanda, Susanna, Kayleigh, Thirza, Marja, Lotte, dank voor de ontzettend fijne samenwerking de afgelopen jaren. Met Sporten voor Sophia vorig jaar natuurlijk als absoluut hoogtepunt! Conny en Hester, dank dat ik altijd met alle chirurgische vragen bij jullie terecht kon. Marjolein, dank voor de fijne samenwerking, onder andere bij het opzetten van het groot onderzoek. Ik bewonder al jouw inzet voor het psychosociale deel van onze poli! Susanna, Kayleigh en Thirza, dank voor jullie flexibiliteit en praktische hulp wanneer ik weer een bepaalde meting wilde doen of extra bloed wilde verzamelen. Joanne, heel erg bedankt voor al je hulp, vanaf het moment dat ik als student langs kwam om data te verzamelen, tot het laatste jaar waarin we urenlang alle voedingen samen hebben berekend. Wendy, ontzettend leuk om te zien dat jij ook steeds enthousiaster bent geworden over het darmfalen onderzoek! Dank voor je hulp bij een deel van de Trompet studie. Marja, dank voor alle logistieke hulp tijdens de poli, maar vooral alle gezellige momenten achter de balie! Lotte, wat een verademing was het dat jij de laatste maanden het onderzoek kwam overnemen. Jij hebt er voor gezorgd dat ik het onderzoek met een gerust hart kon overdragen. Ontzettend

knap hoe je al allemaal mooie projecten hebt opgezet, over een paar jaar sta jij gewoon hier!

Collega's van de afdeling Kinder-MDL, Lissy, Martha, Merel, Dwight, Maarten, Gertrude, Myrthe, Martine, dank voor de leerzame en gezellige jaren. Martine & Myrthe, dank voor alle gezellige momenten, in het bijzonder de gezellige ESPGHAN congressen die we samen bezocht hebben, op naar onze reünie over 5 en 10 jaar ;-) Gertrude, fijn dat we tijdens de laatste loodjes nog veel dingen konden overleggen, dank daarvoor!

Collega's van de afdeling Kinderchirurgie, alle kinderchirurgen, Claudia, John, Pim en Marco, en alle verpleegkundig specialisten, Klarieke, Irene, Nicole, Sanne en Elvira, dank dat ik bij jullie een groot deel van mijn onderzoek mocht doen.

Sabrina, Jolande, Willie en Marja, ook jullie wil ik bedanken! Wat een geluk dat ik jullie allemaal iets kon vragen, wanneer ik dat nodig had. Dankzij jullie hulp werd er altijd wel weer een gaatje gevonden in de agenda van de twee professoren en werden alle formulieren weer op tijd van een handtekening voorzien. Maar vooral dank voor al jullie interesse en support.

Alle collega's van het laboratorium Kindergeneeskunde, dank voor de afgelopen jaren. Janneke, dank voor het mogelijk maken van ons onderzoek op jouw lab. Rolien en Marcel, dank voor al jullie praktische hulp.

Alle verpleegkundigen van 1 zuid, ICN, ICK en Pallieterburght, dank voor al jullie moeite om de samples te verzamelen en metingen te doen! Saskia Gischler en Cindy Joosen, bedankt voor de fijne samenwerking met Pallieterburght/ICK transitie tijdens het doen van dit onderzoek!

Jorine, dank voor de fijne samenwerking de afgelopen jaren, ideaal dat we zo allebei met een gerust hart op congres of vakantie konden gaan. Dank voor al je hulp bij het overnemen van metingen, en alle gezellige momenten wanneer we weer een PEAPOD of BODPOD meting probeerden te doen bij één van de patiënten.

Laura, Kirsten en alle endocrinologie researchverpleegkundigen, dank voor de samenwerking! Kirsten, dank voor je flexibiliteit als er weer eens een PEAPOD meting tussendoor kon gaan.

Beste Merit & Cora, dank voor de fijne samenwerking de afgelopen jaren. Dankzij jullie kon het onderzoek uitgebreid worden naar Amsterdam en hebben we zo nog meer patiënten weten te includeren. Dank voor een kijkje in de keuken bij jullie team en betrokkenheid bij het onderzoek. Hedy, ook jij bedankt voor de fijne samenwerking de afgelopen jaren!

The laboratory of Human Nutrition in Glasgow; Ben, I cannot thank you enough for all the effort you put in all the bio-informatics! Vaios, many thanks for all the help when I was in Glasgow. Rodanthi, thank you for all the analyses you did for our project.

Uiteraard ook alle coauteurs, veel dank aan jullie bijdrage aan de artikelen. Zonder jullie was mijn proefschrift er niet geweest. Dimitris Rizopoulos, dank voor je hulp bij statistische analyses. Ko Hagoort wil ik bedanken voor de revisies tijdens de laatste fase van mijn onderzoek.

Alle studenten die de afgelopen jaren mee hebben geholpen aan één of meerdere projecten: Leslie Strengers, Noortje Rijnen en Bo van Schijndel, dank voor jullie inzet en hulp bij het verzamelen van alle gegevens en samples!

(Oud)collega's van de Z-flat en de Na-toren, zonder jullie was het onderzoek doen zeker niet zo leuk geweest. Dank voor alle leuke momenten! Lieve Roos, wat een geluk dat wij heel wat jaren bij elkaar op de kamer mochten door brengen! Ontelbare koffietjes, af en toe een vrijdagmiddagborrel, WK-versiering en -poultjes! Dank voor het luisterend oor, het relativeren, maar bovenal alle gezelligheid! Wat bijzonder vond ik het om jouw paranimf te mogen zijn! Marianne, dank voor de altijd gezellige koffietjes, de motivational talks en ook de gezellige momenten buiten het EMC!

Alle Sophia onderzoekers bedankt voor de gezelligheid tijdens de borrels, diners en (ski) trips! In het bijzonder mijn SOV-bestuursgenootjes, Manouk, Robin, Lisette, Jennifer, Bianca en Paola, dank voor alle gezellige vergaderingen, activiteiten en borrels!

Alle kinderartsen en verpleegkundig specialisten van het Maasstad ziekenhuis: Annelies, Desiree, Frank, Helene, Ingrid, Jennifer, Johan, Jurjen, Marieke, Mariël, Marjolijn, Martin, Michael, Richard, Rick, Riwka, Sandra, Xandra, dank voor alle leerzame en gezellige momenten. Na 4 jaar onderzoek doen was het even wennen in de kliniek, maar jullie hebben er voor gezorgd dat ik mij direct thuis voelde, dank daarvoor! Alle arts-assistenten: Chantal, Emma, Ilse, Iris, Iris van M, Jasmina, Joeri, Kimberley, Lauren, Leonore, Lieneke, Martine, Maureen, Michelle, Nienke, Pieter, Robin, Selma, Tara, dank voor alle gezellige momenten in en buiten het Maasstad!

Dit boek is indirect ook mede mogelijk gemaakt door mijn vriendinnen, vrienden en familie, dank daarvoor! In het bijzonder wil ik bedanken:

Alie, Astrid en Elly, lieve oudste vriendinnetjes, inmiddels al meer dan 15 jaar! Wat bijzonder dat we elkaar al zo lang kennen. Op naar de volgende 15!

Lieve Rose en Klaziena, hoe bijzonder is het dat we straks allemaal gepromoveerd zijn? Gelukkig was er nog genoeg tijd voor weekendjes weg, avonden eten en andere mooie momenten! Bedankt voor jullie vriendschap!

Lieve Tess, Rianne, Annefleur, Ellen, Sip, dank jullie wel voor alle gezellige momenten! Ook al wonen we allemaal ver van elkaar vandaan, het is altijd gezellig om elkaar weer te zien, en ik hoop dat we nog veel mooie momenten met elkaar mogen meemaken! Tess en Ri, dank voor alle mooie reizen samen!

(Beach-)volleybal teamies, dank voor alle afleiding naast het werken. Heerlijk om mensen buiten het ziekenhuis te leren kennen in Rotterdam en af en toe even helemaal niet met werk bezig te hoeven zijn.

En dan mijn paranimfen. Lieve Lin, we leerden elkaar kennen via ons promotieonderzoek, maar al snel volgden er meer afspraken buiten dan in het ziekenhuis ;-) Dank voor de momenten dat je tijdens mijn congressen en vakanties samples hebt verzameld. Fijn dat we altijd even konden sparren, over onderzoeksdingen, maar juist ook over vele andere onderwerpen. Op naar nog vele dinertjes en biertjes samen!

Lieve Lis, er was geen twijfel over mogelijk dat ik jou zou vragen om mijn paranimf te zijn. Vriendinnen vanaf letterlijk het 1e uur van Geneeskunde. Wat was het bijzonder om jouw paranimf te mogen zijn. Dank voor je onvoorwaardelijke steun, je altijd luisterend oor en alle gezellige momenten.

Lieve Torsten, dank voor al je steun. Het moet niet altijd makkelijk geweest zijn mij in deze drukke fase te leren kennen ;-) Werken is leuk… maar samen met jou zijn nog leuker! Op naar nog meer mooie avonturen in en buiten Rotterdam! Nu eerst op naar Costa Rica!

Lieve San, mijn grote kleine zus! Wat heerlijk dat we allebei iets totaal anders zijn gaan doen. Wat ben ik trots op jou. Altijd op de momenten dat ik het nodig had, liet je me weten dat je aan mij dacht. Dank voor al je steun, interesse en alle gezellige momenten. Ik zal de vakantie na mijn congres in New York nooit vergeten!

Lieve pap en mam, jullie kan ik niet genoeg bedanken. Dank voor jullie onvoorwaardelijke steun. Ook al was het hele onderzoekswereldje jullie totaal niet bekend, jullie waren altijd geïnteresseerd en even enthousiast. Heerlijk om bij jullie thuis even totaal niet met onderzoek of het ziekenhuis bezig te zijn. Zonder jullie was dit proefschrift er nooit op deze manier geweest! Dank voor alles!