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.

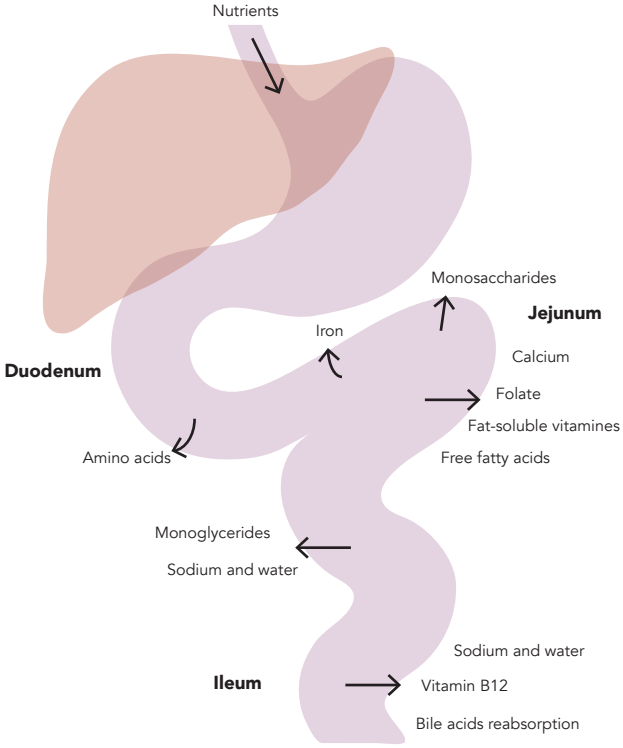
GENERAL INTRODUCTION

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

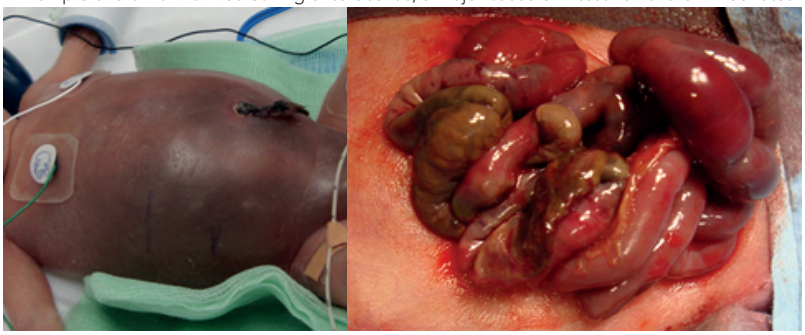


Table 1. Conditions leading to intestinal failure in children. Adapted from[2,13,14]

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]

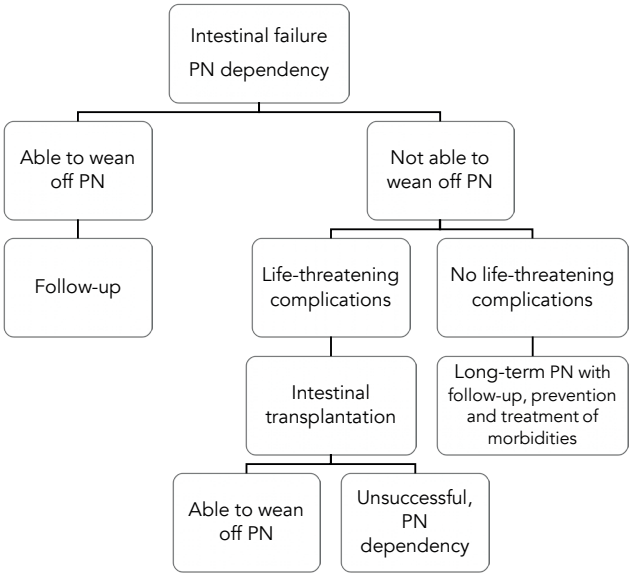
Surgical management of intestinal failure

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

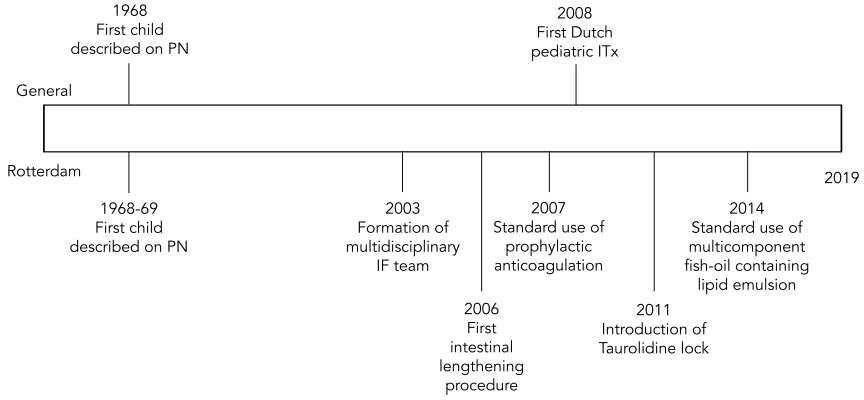


Abbreviation: PN, parenteral nutrition.

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



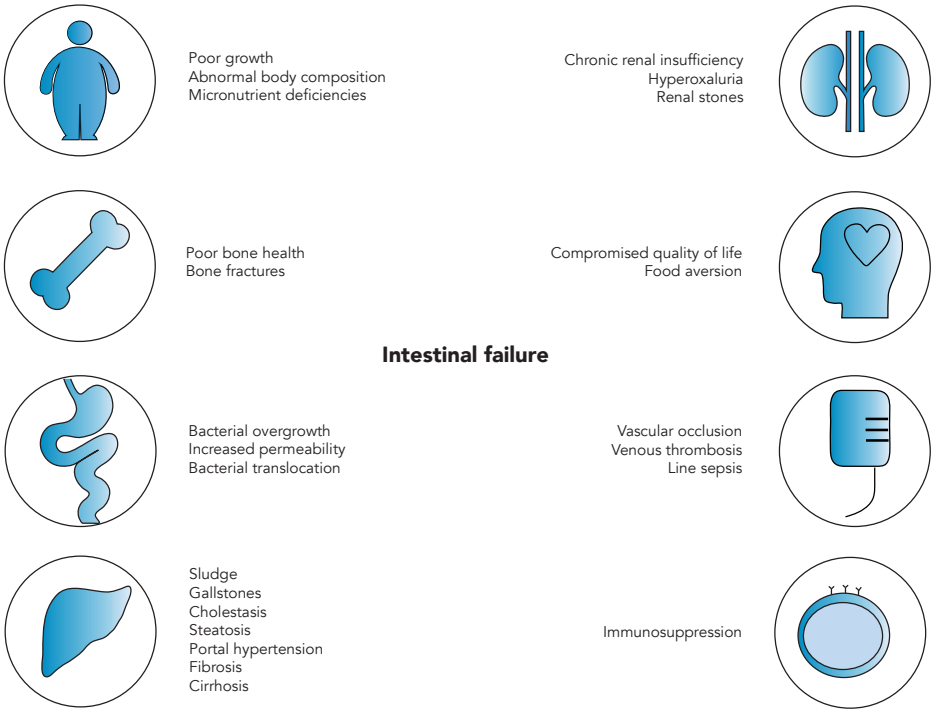
Abbreviations: IF, intestinal failure; ITx, intestinal transplantation; PN, parenteral nutrition.

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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