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.

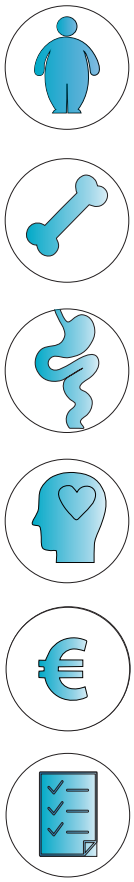
MORBIDITIES RELATED TO INTESTINAL FAILURE

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.

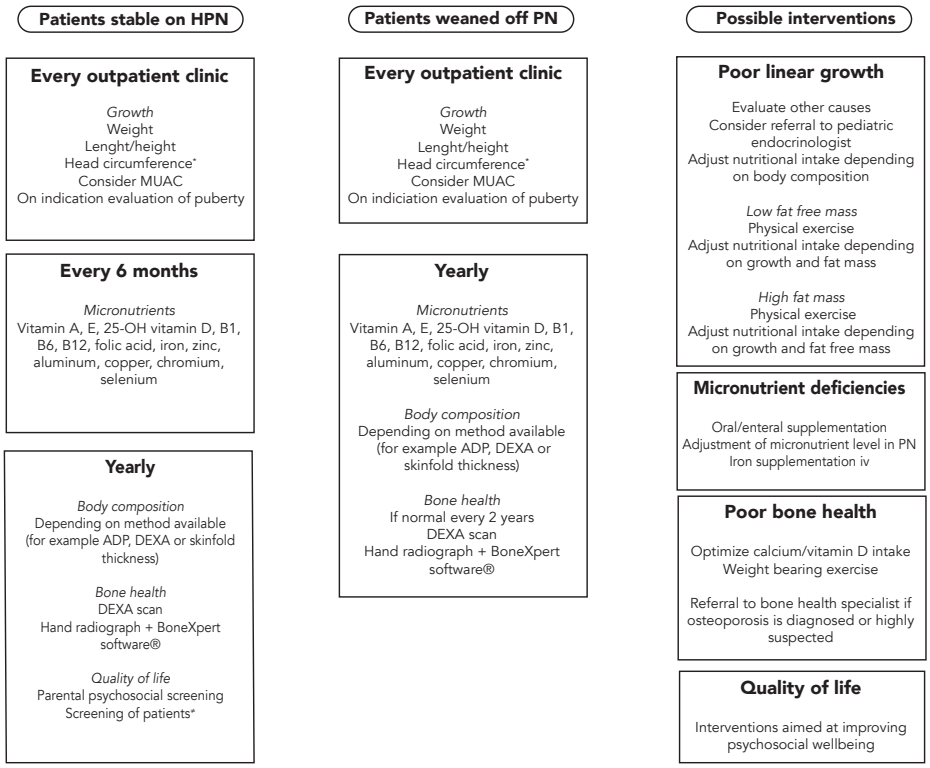
PROPOSAL FOR CLINICAL FOLLOW-UP

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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