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REVIEW ARTICLE

Monitoring of long-term parenteral nutrition in children with intestinal failure

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Abstract

Pediatric intestinal failure (IF) is a rare and complex condition associated with significant morbidity and mortality. It is defined as the reduction of gut mass or function below the minimal needed for absorption of nutrients and fluid to sustain life and growth. Since the advent of specialized multidisciplinary intestinal rehabilitation centers, IF management has considerably evolved in the last years, but serious complications of long-term parenteral nutrition (PN) can occur. Main complications include intestinal failure-associated liver disease, growth failure, body composition imbalance, central venous access complications, micronutrient deficiencies and toxicities, metabolic bone disease, small intestinal bacterial overgrowth, and renal disease. With improvement in survival rates of patients over the last 20 years, emphasis should be on limiting IF-related comorbidities and improving quality of life. Close monitoring is pivotal to ensuring quality of care of these patients. The care of children with chronic IF should involve a comprehensive monitoring plan with flexibility for individualization according to specific patient needs. Monitoring of children on long-term PN varies significantly across units and is mainly based on experience, although few guidelines exist. This narrative review summarizes the current knowledge and practices related to monitoring of children with IF. The authors also share their 20-year experience at the Royal Children's Hospital in Melbourne Australia on this topic.

Introduction

Intestinal failure (IF) is due to functional or anatomic loss of bowel and is characterized by insufficient absorption of nutrients and fluid requiring parenteral support to sustain life and achieve growth.[1,2] Long-term parenteral nutrition (PN) is the cornerstone of therapy in chronic IF. Since the first patient was sent on home PN in the late 1970s,[3] considerable progress has been accomplished in the field of pediatric IF supported by multidisciplinary intestinal rehabilitation programs and advances in medical and surgical care.[1] Despite these achievements, long-term PN can still result in life-threatening complications. As the new generation of children with IF can expect to survive longer, an increased emphasis on optimization of quality of life and prevention of morbidity is needed.

Attention to close monitoring of patients on long-term PN with adjustment of nutritional and non-nutritional therapies accordingly is key to optimizing their outcomes. There is a wide variability in practices across IF centers in terms of monitoring these complex patients and limited data to guide the development of evidence-based recommendations.[1,4] Available guidelines include the joint guidelines from the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) and the European Society of Parenteral and Enteral Nutrition (ESPEN) published in 2005[5] and updated in 2018[6–10] and the American Society for Parenteral and Enteral Nutrition recommendations published in 2017.[11]

This paper aims to provide a narrative review of the literature on monitoring of children (<18 years of age) with IF on long-term PN therapy (>4 weeks). The authors used a PubMed search of original papers, review articles, and society guidelines up to July 2018. Relevant papers were selected to formulate an overview of the topic. We focused on papers describing monitoring (i) growth and body composition; (ii) laboratory assessment; and (iii) long-term complications. This paper is mainly intended for home PN children but could also serve as a guide for inpatients receiving PN for >4 weeks. The surveillance may need to be individualized according to clinical judgment.

Growth and body composition monitoring

Growth monitoring. As children with IF are totally or partially dependent on parenteral caloric supply, there is a risk of iatrogenic underfeeding and overfeeding. The aim for growth in these children should be based on normal growth criteria, and weight should be proportional to height.[12,13] The genetic target

height based on mid-parental height should be factored into expectations for growth.[12,13] Growth failure, particularly short stature, has been reported in long-term PN.[1,2,12–16] Stunting may be due to chronic intestinal inflammation, poor nutritional intake at critical periods, the underlying disease itself, and side effects of medications.[12,13] The contribution of endocrine-related influences should be excluded.

Once discharged from hospital, growth is monitored at each outpatient follow-up. This should be monthly or more frequently in infants but could be extended to every 3 months in older children with stable home PN requirements.[5,7] More frequent monitoring is indicated during changes in PN prescription or while weaning PN. Weight-for-age, height-for-age, head circumference (for children <3 years), weight-for-height (if <2 years), and body mass index (if >2 years) are plotted on appropriate growth charts and converted to *Z* scores.[11]

PN requirements should be regularly re-evaluated and calories adjusted according to growth and EN advancement.[11] A reduction in the number of days PN is infused is encouraged as soon as possible rather than gradually reducing daily energy intake.[5] In case of excessive weight gain without longitudinal growth, energy intake should be reduced.[5,17]

Body composition monitoring. As the measurement of weight alone can mask sarcopenia, the assessment of body composition should be part of routine evaluation.[18] Children with IF have been reported to have abnormal body composition with low lean mass and high fat mass.[14,18] Low lean body mass may result in muscle weakness and reduced bone accretion.[17] High fat mass may be associated with long-term cardiovascular and metabolic risks.[17] Reduced physical activity, inappropriate nutritional supply, and chronic inflammation may all contribute to abnormal body composition in children receiving long-term PN.[17,18]

Dual-energy X-ray absorptiometry (DXA) can provide an accurate assessment and distribution of fat mass and lean body mass. It is usually performed in children over the age of 5 years (cooperative children) every 1–2 years but may not be available in all centers.[7,17] Measurement of triceps' skinfold thickness and mid-upper arm circumference can be used as a noninvasive bedside measurement of body composition.[18,19] Serial measurements every 3–6 months can provide a trend over time and thus a dynamic picture. PN energy and protein intake should be adjusted in children with abnormal body composition with the aim to target the body composition of a healthy child of the same age.[17] Physical activity, essential for building muscle mass, should be regularly assessed and encouraged. Low levels of motor proficiency can impact participation in physical activity and fitness,[20] which may further contribute to a cycle of reduced muscle bulk and weakness. The presence of a central catheter and enterostomies may be a barrier to physical activity for some parents.

Long-term laboratory monitoring

Laboratory monitoring is aimed at detecting nutrient deficiencies and toxicities.[5] The critical periods for nutrient imbalances are during periods of rapid growth, physiological stress, and during the transition from PN to enteral diet.[1,2,21] The administration of intravenous vitamins and trace elements bypass the normal regulatory mechanisms present in the gut, resulting in toxicity risk.[5,22] The loss of specific intestinal segments predisposes to certain micronutrient deficiencies.[23] Although adequate weight gain may be achieved, children may still exhibit features of micronutrient deficiencies.

Table 1 Impact of acute-phase response on serum micronutrient values

Micronutrients	Effect of acute-phase response
Trace elements	
Copper	Increased
Iron	Decreased
Ferritin	Increased
Zinc	Decreased
Plasma Selenium	Decreased
Chromium	Decreased
Manganese	No effect
Vitamins	
Vitamin A	Decreased
Vitamin C	Decreased
Vitamin D	Decreased
Vitamin E, K, B12, B1	No effect

An important challenge for the assessment of micronutrient status is that circulating serum levels may not reflect body stores of many micronutrients.[3] Given that tissues biopsies are too invasive, more reliable markers need to be established for an accurate assessment of micronutrient status. Another important consideration is that most micronutrients are acute-phase reactants resulting in variability in serum levels during active inflammation with falsely low or high levels[24–27] (Table 1). Therefore, assessment of serum micronutrients should be avoided during periods of stress and be accompanied by measurement of the C-reactive protein level to assist in the interpretation of results. The impact of the transfusion of blood products on micronutrient levels is unclear. In our practice, measurement of micronutrient levels is generally deferred by 3–4 weeks (and up to 3 months if an erythrocyte marker is used) after the receipt of a blood transfusion to avoid any misinterpretation of micronutrient status. In addition, the timing of laboratory assessment relative to the timing of PN infusion may be important to consider. It is unknown how long micronutrients infused intravenously must be stopped to ensure a blood value is interpretable.[3]

Laboratory monitoring should be routinely conducted in all long-term PN patients and may need to be specifically tailored to account for individual pathologies and risks.[4] The articles consulted for this review have demonstrated a wide variability in laboratory monitoring in long-term PN across centers in terms of markers used and frequency of monitoring. A survey conducted in 14 American intestinal rehabilitation centers has also pointed out this inconsistency.[1]

Monitoring trace elements and minerals supplementation. Monitoring of trace elements and minerals is presented below based on a practical approach.

Children with high gastrointestinal losses. In addition to the routine PN monitoring, children with high gastrointestinal

losses are at risk of significant loss of macro- and micronutrients and therefore require specific consideration. These children generally lose high quantities of sodium within the effluent, resulting in total body sodium depletion, dehydration, and poor growth.[1] Stool or effluent sodium measurement can assist in quantifying these losses. Urine sodium measurement assesses the conservation of total body sodium. It is performed every 1–3 months and should be aimed at achieving a urine sodium level of >20 mmol/L, with a urine Na/K ratio >1.[13,28] Children with short bowel syndrome and high gastrointestinal losses are also at risk of acid–base imbalance, even more if they have renal impairment or receive high protein loads.[29] Blood gas monitoring is generally included in routine laboratory panels every 1–3 months.

Magnesium depletion is very common in children with high gastrointestinal losses. Besides malabsorption due to short bowel, magnesium binds with unabsorbed fatty acids and is lost in the effluent.[30] Furthermore, if sodium depletion is not corrected, the kidneys will reabsorb sodium at the expense of magnesium and potassium excretion.[30] Serum magnesium is monitored every 1–3 months and supplemented accordingly. Zinc is mainly excreted in feces, and patients with high gastrointestinal losses may require additional supplementation in PN.[9,26] Serum zinc level is routinely monitored every 6 months or more frequently in case of high gastrointestinal or cutaneous losses.

Children with cholestasis. Copper and manganese are both excreted in the bile.[25] Hence, they should be carefully monitored in case of cholestasis to avoid accumulation and toxicity.

Copper is commonly reduced or removed from PN solutions administered to cholestatic patients.[9,25] However, copper deficiency has been described with copper-free PN.[1] Patients with high proximal gastrointestinal losses, such as jejunostomies, or other high biliary output may have higher copper requirements.[1,5,9] Serum copper and ceruleoplasmin should be monitored every 6 months and copper supplementation adjusted accordingly.[11]

Manganese toxicity seems to be a greater concern than deficiency given that manganese is a PN contaminant with potential neurotoxicity and virtually no deficiency reported.[4,22,25] There are reports of toxicity resulting from hypermanganesemia in pediatric patients, and postmortem data in home PN patients have shown high manganese levels in tissue samples.[31] Some authors claim that manganese contamination of PN solutions is sufficient to meet the daily requirements of parenterally fed children without the need for additional manganese supplementation.[22,25,31] As central nervous system deposition of manganese can occur without symptoms, regular monitoring of whole blood manganese level[4,22] is recommended every 6–12 months, with magnetic resonance imaging in cases of suspected toxicity.[22] Young children with cholestasis are at the highest risk of toxicity. It is commonly agreed that manganese supplementation should be removed in cholestatic patients.[4,9,22] However, as manganese and copper are part of a fixed-concentration, multitrace element solution, this makes it very difficult to adjust/remove the dose without impacting on other trace elements. In view of the above, there is a need to reformulate multitrace element solutions with a lower manganese concentration. Formulation of individual trace element additives may be helpful for selected patients. Contamination levels of manganese in PN should be documented on PN solutions.[31]

Children with no or minimal enteral nutrition. Monitoring and supplementation of carnitine remains controversial.[5,32] Carnitine is required for the transport of long-chain triglycerides across mitochondrial membrane for oxidation.[4,32] It is ubiquitous in oral diet but is not routinely supplemented in PN solutions.[4,8,32,33] Children can endogenously synthesize some carnitine; however, neonates have limited stores.[32] A PN-dependent child with no enteral feeds can develop low serum carnitine levels within weeks, with the potential to impact energy utilization and impair growth.[4,32,33] However, there has been no evidence of benefit of carnitine supplementation on short-term outcomes (weight gain, lipid utilization) according to a Cochrane review.[32] Monitoring of plasma carnitine should be considered in patients on PN for >4 weeks,[8,11] conducted every 6 months. Routine supplementation of preterm and young infants <5 kg on PN has been suggested.[34]

Iron is not routinely included in PN due to compatibility concerns, anaphylaxis risks, and iron overload risk.[5,9] Patients on long-term PN are consequently at risk of iron deficiency[25] if oral supplementation is not feasible. Options for the prevention and treatment of iron deficiency include regular intermittent iron infusions or a maintenance daily dose of iron dextran in PN.[9] It is generally stated that iron dextran is incompatible with lipids or all-in-one admixtures causing coalescence of lipid droplets,[9] although one report suggests no evidence of physical incompatibility.[35] A potential approach to address this issue is to include iron dextran in PN on nonlipid day(s). There are anecdotal reports of patients receiving maintenance dose of iron dextran in all-in-one admixtures without any reported issues. More research is needed in this area. Iron studies (ferritin, transferrin saturation, transferrin receptors) and full blood count should be conducted every 3–6 months to assess iron stores.

Iodine deficiency has been reported, particularly with iodine-free PN use.[34–36] Monitoring by urinary iodine excretion and serum thyroid-stimulating hormone level is suggested as part of an annual assessment or more frequently as required.[5,11,36]

Molybdenum is not included in the Australasian Society of Parenteral and Enteral Nutrition pediatric trace element solution. ESPGHAN/ESPEN recommend molybdenum supplementation for children on long-term PN.[9] However, there are no reports of clinical molybdenum deficiency,[9] likely due to external contamination of PN solutions. Biochemical markers of Molybdenum status are not available.

Routine addition or monitoring of other trace elements, including fluoride, boron, and silicon, is not currently recommended.[37]

Children with renal impairment. As patients with renal impairment may not be able to excrete selenium, chromium, zinc, and molybdenum, close monitoring may be required in this setting.[5,25,26] Chromium supplementation is no longer required as chromium contaminates PN solutions to a degree that satisfies requirements.[5,9] In children receiving home PN with chromium supplementation, high serum levels have been reported, and autopsy data showed high tissue chromium concentrations.[38] There are also concerns about potential nephrotoxicity.[38,39] Unfortunately, serum chromium levels are not a highly reliable

marker of chromium body status; however, they are routinely recommended every 6–12 months to provide an insight into chromium levels.[5]

Selenium deficiency is reported in home PN patients without supplementation, while selenium toxicity has not been reported in children.[9] Routine measurement of serum/plasma selenium is recommended every 6–12 months[11] or more frequently in case of renal impairment. More accurate measures of selenium status exist, such as plasma or erythrocyte glutathione peroxidase and hair and nail selenium levels, but these are often not readily available.[9,26]

Monitoring of vitamins supplementation. Monitoring of water-soluble vitamins is generally restricted to vitamin B12 and folate (using serum folate or red cell folate) as deficiencies and toxicities are rare.[5] However, they are required daily, body stores being limited, except for B12.[10] Vitamin B12 requires close monitoring in children with ileal resection on partial PN. Measurement of total serum B12 has poor sensitivity and specificity in predicting vitamin B12 status.[40] Active B12 (holotranscobalamin) is a more sensitive marker that measures only the part available for the cell use and is recommended every 6–12 months[40,41] in patients with stable PN requirements and more frequently in children weaning from PN. Serum methylmalonic acid and homocysteine are useful to confirm deficiency.[41] In case of shortage of pediatric vitamin preparations, adult formulations should not be used as they can contain components associated with death in infants.[10]

Deficiencies in fat-soluble vitamins are reported in children on long-term PN;[42] hence, their monitoring is advised.[11] With the advent of the new-generation lipid emulsions (SMOFlipid and Omegaven), vitamin E provision in PN has considerably changed. The vitamin E content of Intralipid and Clinoleic is, respectively, 13 mg/L and 30 mg/L compared to approximately 200 mg/L in SMOFlipid and Omegaven (Table 2).[43,44] This has resulted in an increase in vitamin E levels, a potent antioxidant, with better liver protection and other beneficial effects.[5,10] However, serum vitamin E levels above 3.5 mg/dL (80 μmol/L) increase the risk of sepsis and necrotizing enterocolitis in preterm infants, although these levels are also reported to reduce the risk of intracranial hemorrhage and severe retinopathy.[5,10,45,46] The recommended parenteral dose of vitamin E in children is 2.8–3.5 mg/kg/day up to a maximum of 11 mg/day.[10,46,47] Vitamin E dose provided by new lipid emulsions combined with fat-soluble vitamin preparations exceed these recommendations for some neonates. Regular monitoring using serum vitamin E level and vitamin E/lipid ratio is advised every 6–12 months in children and more closely in neonates. Safe blood levels are 23–46 μmol/L in premature infants and 11–35 μmol/L in children.[45,46] More trials are necessary to determine safe parenteral doses for children and determine whether the available intravenous multivitamin solutions designed in the era of old-generation lipid emulsions need to be reviewed to avoid vitamin E excess in neonates.

Table 2 Comparison of composition of main intravenous lipid emulsions

	Intralipid	Clinoleic	SMOFlipid	Omegaven
Soybean (%)	100	20	30	0
MCT (%)	0	0	30	0
Olive oil (%)	0	80	25	0
Fish oil (%)	0	0	15	100
Phytosterols (mg/L)	348	327	47.6	0
Alpha-tocopherol (vitamin E) (mg/L)	14	30	160–230	150–296
LA (%)	50	18.5	21.4	4.4
ALA (%)	9	2	2.5	1.8
EPA (%)	0	0	3	19.2
DHA (%)	0	0	2	12.1
ARA (%)	0	0	0.15–0.6	1–4

ALA, alpha-linolenic; ARA, arachidonic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; LA, linoleic acid; MCT, medium-chain triglycerides.

It is thought that parenteral vitamin D requirements might be lower than enteral requirements as no enteral intake of minerals needs to be facilitated.[5] However, suboptimal 25-OH vitamin D levels have been reported in children on long-term PN in 40% despite receiving appropriate fat-soluble vitamin solutions.[15,42,48] In our experience, suboptimal levels of vitamin D (<50 nmol/L) are encountered in our cohort despite administration of 200–400 IU/day. Children receiving long-term PN should be monitored periodically for vitamin D deficiency; a serum 25-OH vitamin D concentration >50 nmol/L indicates sufficiency.[10] In patients requiring additional vitamin D supplementation, enteral or parenteral supplementation is considered. Some children with IF may not achieve sufficient levels on enteral vitamin D supplementation. However, intravenous form of vitamin D is not commonly available, and acceptability of an intramuscular injection may be difficult. Further research is needed to determine the optimal vitamin D dose in this population.

Vitamin A status can be assessed every 6–12 months by serum concentrations of vitamin A, serum retinol, or the concentration of retinol binding protein depending on local availabilities.[10] Vitamin K status is assessed using international normalized ratio every 3 months. Proteins Induced by Vitamin K Absence II (PIVKA-II) seem to be a useful biomarker of subclinical vitamin K deficiency for at-risk patient groups and should be used when locally available.[10]

Monitoring of intravenous lipid emulsions provision. Lipid clearance is verified by serum triglyceride level, preferably before the beginning of the cycled PN.[8] Assessment is performed every 1–3 months in stable patients. Patients at high risk of hyperlipidemia, that is, patients with high lipid or glucose dosage, sepsis, malnutrition, or extremely low birth weight infants, need frequent monitoring.[8] ESPGHAN/ESPEN recommend a serum triglyceride level <2.8 mmol/L in neonates and <4.5 mmol/L in older children as lipoprotein lipase is saturated at around 4.5 mmol/L.[5,8,49] Manufacturers of intravenous lipid emulsions (SMOF, Clinoleic, Omegaven) recommend a maximum level of 3 mmol/L. However, it seems acceptable to cautiously tolerate a triglyceride level up to 4.5 mmol/L in older children in order to provide critical energy intake and to prevent essential fatty acids deficiency (EFAD). Reduction of lipid dosage is recommended if triglycerides levels are above the limits defined or in case of severe unexplained thrombocytopenia.[8]

Markers of liver function should be monitored as mentioned in the corresponding section.[8]

To prevent EFAD, a minimum linoleic acid intake of 0.25 g/kg/day in preterm infants and 0.1 g/kg/day in term infants and older children is recommended, which also supplies adequate amounts of linolenic acid.[8] Patients are at risk of EFAD if they receive lipid-free PN or if they are lipid-restricted below the minimum mentioned and without sufficient enteral intake.[4] Routine monitoring is recommended annually in patients receiving long-term PN as EFAD deficiency has been reported in this population.[1,13] More frequent monitoring is required if the patient is at increased risk of EFAD as mentioned above. Monitoring includes fatty acid profile with triene/tetraene ratio.[1] Oral and cutaneous sunflower and safflower have been reported to reverse EFAD and may be an option in patients where intravenous and enteral supplementation is not possible or limited.[30]

Monitoring of long-term complications

Intestinal failure-associated liver disease. Intestinal failure-associated liver disease (IFALD) is the most frequent complication in children on long-term PN.[4,15,43,49] Although some hepatic complications can be reversible, severe outcomes with end-stage liver disease may occur.[6,43,49] All efforts should be undertaken to identify the disease at an early stage where medical interventions could improve or limit its extent.[43,49] With the advent of the new generation of lipid emulsions and implementation of hepatoprotective strategies, the presentation of IFALD has changed in the last years, from a predominant cholestatic picture with high bilirubin to a presentation dominated by portal hypertension signs with normal or mildly raised bilirubin.

Therefore, IFALD definitions based mainly on bilirubin level are no longer valid as they do not include all IFALD cases. In our experience, none of our home PN patients have abnormal bilirubin levels, although some of them have a histological diagnosis of IFALD with (advanced) portal hypertension. The definition of the new face of IFALD should encompass the usual clinical, biological, and radiological parameters but without bilirubin/cholestasis being necessarily the predominant marker. Other potential causes of deranged liver function tests (LFT) must be excluded, including viral hepatitis and sepsis.

Pathogenesis of IFALD is multifactorial.[1,4,5,11,15,22,49,50] The nutrition-related factors include absence of enteral feeding, overfeeding, excess of lipid or glucose intake, imbalanced amino acids composition, continuous PN (non-cyclical), lipid emulsions containing high w-6/w-3 ratio and high phytosterols with low α-tocopherol levels, and micronutrient toxicity (copper, manganese, iron, aluminum). An absolute or relative carnitine deficiency is also believed to contribute to steatosis.[49] Non-nutrition-related factors include recurrent sepsis, prematurity, bacterial overgrowth, interruption of enterohepatic circulation, and hepatotoxic medications.

LFT are the usual noninvasive blood marker used for monitoring of IFALD, including alanine aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, and bilirubin. However, one should bear in mind that LFT do not always correlate with the stage of liver disease: some children with advanced IFALD have minor LFT derangements.[49] Monitoring of white cells and platelets counts, coagulation screen, and albumin levels is performed to assess synthetic function and portal hypertension progress. Albumin may be low because of inflammation or protein-losing enteropathy. The frequency of long-term monitoring is usually 1–3 months depending on the patient's condition. Glucose levels are also monitored regularly, and HbA1c is recommended annually. Alpha-fetoprotein is suggested annually in patients with cirrhosis and ammonia in end-stage IFALD. The aspartate aminotransferase-to-platelet index has not been helpful in predicting the degree of fibrosis in children with IFALD but may be useful in predicting cirrhosis.[49,51]

Abdominal ultrasound is usually performed annually to check liver echotexture and size, signs of portal hypertension, and eventual gallstones.[5] Liver biopsy and endoscopic screening for varices are performed case by case after consultation with a gastroenterologist or hepatologist.[15] Liver biopsy is an invasive procedure that may be inaccurate in assessing the type and severity of IFALD due to patchy liver disease.[49] However, it may not change patient management and should be limited to selected cases.[43] Transient elastography (Fibroscan) is not validated in this population but could be used for individual follow-up.[49]

Intestinal failure-associated metabolic bone disease. Intestinal failure-associated metabolic bone disease (IF-MBD) is reported in 30–83% of children receiving long-term PN, with low bone mineral density, bone pain, and fractures.[12,15,19,52–55] The etiologies are likely multifactorial: inadequate supply of calcium, phosphate, and vitamin D; use of steroids and diuretics; underlying disease; chronic inflammation; chronic acidosis; aluminum and vitamin D toxicity; hypercalciuria; and lack of physical activity.[6,12,14,15,52,53,55–57] Vitamin K deficiency and prophylactic oral anticoagulation by warfarin may be linked to low bone mineralization.[56,58]

DXA is considered the golden standard for diagnosis and monitoring of MBD from the age of 5 years[52,55] and is repeated every 1–2 years.[5,11] Monitoring of biochemical markers of bone metabolism include serum 25-OH vitamin D, alkaline phosphatase, phosphate, plasma and urinary calcium, and parathyroid hormone.[5,6] The impact of IF-MBD on quality of life, physical activity, and lean mass can be important in some patients, highlighting the importance of prevention. An annual review by a pediatric endocrinologist is recommended to assess bone health, stature, and identify risk of delayed puberty.[52]

The contamination of aluminum in PN solutions has been a concern as aluminum toxicity can cause bone disease, neurological impairment, liver disease, and anemia even years after initial exposure.[50,57,59–61] Although aluminum content in PN has significantly decreased in the last years, high aluminum levels are still reported in children receiving PN.[59,62,63] Calcium and phosphate salts and multivitamin and trace element solutions are now the primary sources for aluminum contamination in PN.[56,57] The US Food and Drug Administration has advised that PN solutions are required to contain <25 mcg/L of aluminum with a daily intake of <5 mcg/kg/day.[59,62] PN solutions should be labeled with the maximum aluminum content in home PN patients and in inpatients receiving PN, especially neonates due to immature kidney function. Annual screening of aluminum levels in blood and urine are suggested, avoiding external contamination of samples.[11,12,56,57]

Table 3 Comprehensive monitoring of children on long-term PN[†]

A. Growth, body composition and dietetic monitoring	
Growth	Weight, height, weight-for-height (if <2 years), body mass index (if >2 years), head circumference (if <3 years)
	Monitor every 1–3 months or more frequently in infants
Body composition	DXA: every 1–2 years
	Triceps skinfold, mid-arm circumference, mid-arm muscle circumference: every 3–6 months
Dietetic review	Review of nutrition and fluid requirements
	Assess for possibility of decreasing PN and advancing EN
	Encourage oral feeding, follow-up with a feeding therapist
	Monitor every 1–3 months or more frequently for infants
B. Laboratory monitoring	
Routine tests	*Blood:* Blood gas, sodium, potassium, ionized or corrected calcium, phosphate, magnesium, chloride, urea, creatinine, glucose, LFT, full blood count, coagulation profile, triglycerides
	Urine: Sodium, potassium, osmolality
	Monitor every 1–3 months depending on patient's stability
Vitamins and trace elements	3-6 monthly: Iron studies, 25-OH vitamin D
	6–12 monthly:
	• Vitamin A, vitamin E, vitamin E/lipid ratio, active B12 with methylmalonic acid and homocysteine, folate
	• Zinc, copper and ceruleoplasmin, selenium, manganese, chromium, TSH, and urinary iodine
	Add CRP to assist with interpretation of results
	Postpone blood tests if recent infection/inflammation or transfusion
Other tests	Carnitine: 6 monthly
	Essential fatty acids: annually
	Aluminum: annually
	HbA1 C: annually
C. Monitoring of long-term complications	
IF-associated liver disease	LFT, full blood count: every 1–3 months
	Abdominal US: annually
	Liver biopsy, endoscopy: case by case
	Alpha-fetoprotein: annually if cirrhosis
	Ammonia in end-stage IFALD
	Aspartate aminotransferase to platelet index[‡]: annually
IF-associated metabolic bone disease	DXA: every 1–2 years
	25-OH vitamin D, ALP, calcium, phosphate: every 3 months
	PTH, urine calcium: every 6–12 months
	Physical activity assessment: at each follow-up
	Endocrinology review: annually
IF-associated renal disease	Urea, creatinine: every 1–3 months
	Cystatin C, urine protein, oxalate, calcium: every 6 months
	Renal US, blood pressure: annually
	Nephrology review: annually in case of irreversible intestinal failure
Monitoring of other complications	CVAD: X-ray to check CVAD tip position every 1–2 years; vascular Doppler to assess patency of vessels before new CVAD insertion
	Neurodevelopmental assessment
	Quality of life assessment: at each follow-up
	Audiology review for young children: annually and then as required
	Dental review: annually
	Immunizations including influenza vaccine annually and rotavirus vaccine

[†]Start long-term monitoring in children requiring PN for >4 weeks and not likely to achieve enteral autonomy soon. Monitor more frequently if PN provision has recently changed or in case of renal or hepatic dysfunction or increasing gastrointestinal losses.
[‡]A score > 1.6 correlates with advanced fibrosis.
ALP, alkaline phosphatase; CRP, C-reactive protein; CVAD, central venous access device; DXA, dual-energy X-ray absorptiometry; EN, enteral nutrition; IF, intestinal failure; IFALD, intestinal failure-associated liver disease; LFT, liver function test; PN, parenteral nutrition; PTH, parathyroid hormone; TSH, thyroid-stimulating hormone; US, ultrasound.

Intestinal failure-associated renal disease. IF-associated renal disease is often an unrecognized complication of long-term PN therapy. Renal impairment has been reported to occur in 30–56% of long-term PN patients using an estimated glomerular filtration rate (GFR).[64–68] However, the estimated GFR underappreciates true renal function as creatinine is a poor marker of renal function, especially in the early stages of renal damage,[65,67] even more in presence of low lean body mass. Cystatin C is not related to muscle mass and may be a better indicator of renal function.[66] The measured GFR is the gold standard to assess renal function but is complex in practice.[66] Moukarzel *et al*. found low measured GFR in all long-term PN patients studied, with PN duration being inversely correlated with GFR.[66,68] Persistent proteinuria has also been described in this population.[64]

Although the mechanisms resulting in IF-associated renal disease are not fully understood, several contributing factors have been suggested. Main factors include prolonged dehydration, sepsis, hemodynamic instability episodes, nephrotoxic agents, hyperoxaluria, and prematurity. PN-related factors include

Table 4 Parenteral nutrition monitoring form

Frequency of monitoring	1–3 months	3–6 months	6–12 months	Annual	As required
• Growth	✓				
• Dietetic review	✓				
• Routine bloods: Blood gas, sodium, potassium chloride, calcium, phosphate, magnesium, glucose, urea, creatinine, liver function tests, triglycerides, full blood count, coagulation profile	✓				
• Urine: sodium, potassium, osmolality	✓				
• Physical activity	✓				
• Quality of life	✓				
• MUAC, triceps skinfold, mid-upper arm muscle circumference		✓			
• 25-OH vitamin D		✓			
• Iron studies		✓			
• CRP		✓			
• Vitamins: A, E, vitamin E/lipid ratio, active B12, methylmalonic acid and homocysteine, folate, CRP			✓		
• Trace elements: zinc, copper, CRP, ceruleoplasmin, selenium, TSH, urinary iodine, manganese, chromium			✓		
• Free and total carnitine			✓		
• PTH			✓		
• Cystatin C, urine: protein, oxalate, calcium, creatinine			✓		
• Blood pressure			✓		
• Essential fatty acids				✓	
• Aluminum				✓	
• HbA1 C				✓	
• Abdominal ultrasound (including renal ultrasound)				✓	
• DXA				✓	
• Endocrinology review				✓	
• Nephrology review[†]				✓	
• Audiology review[‡]				✓	
• Dental review				✓	
• influenza vaccine				✓	
• Liver biopsy					✓
• Gastrointestinal endoscopy					✓
• Vascular Doppler					✓
• CVAD tip position					✓
• Alpha-fetoprotein					✓
• Ammonia					✓
• Neurodevelopmental assessment					✓

[†]In case of irreversible intestinal failure.

[‡]Annually initially, then as required.

CRP, C-reactive protein; CVAD, central venous access device; DXA, dual-energy X-ray absorptiometry; MUAC, mid-upper arm circumference; PTH, parathyroid hormone; TSH, thyroid-stimulating hormone.

potential cyclical dehydration induced by cyclical PN, promotion of renal stones by acidity of PN solution, and presence of vitamin C and potential chromium and aluminum toxicity.[15,64,66–68] Moukarzel *et al*. demonstrated a strong inverse correlation between parenteral chromium intake and GFR in home PN children.[39] Chronic intestinal inflammation and chronic low-grade renal inflammation induced by translocated bacterial products may represent independent factors.[64]

Monitoring includes serum creatinine and urea (every 1–3 months) and Cystatin C (every 6 months). Urine tests include protein, calcium, oxalate, and creatinine.[64,67] Urine results may vary depending on the timing of tests. The nocturnal PN schedule may lead to an increased nocturnal loss of electrolytes, particularly calcium.[65] Nocturnal hypercalciuria has been reported with cyclical PN and with high amino acids and sodium concentrations.[56,57,65] Ideally, paired urine and blood samples are obtained as far as possible from the end of the cyclical PN.[67] We suggest monitoring aluminum and chromium levels annually.[67] Monitoring also includes assessment of blood pressure and renal ultrasound conducted annually (nephrolithiasis or increased kidney echogenicity).[67] We suggest an annual review by a pediatric nephrologist in case of irreversible IF.

Increasing awareness about this silent complication may help early detection and limit renal damage. This can be achieved by developing renal-sparing protocols for medications and limiting exposure to potential nephrotoxic components in PN solutions. Nephroprotective therapies (angiotensin-converting enzyme inhibitors) could be tried in case of persistent proteinuria, limiting progression to chronic renal disease.[64] Although IF-associated renal disease may not have a major clinical impact in the early years, the consequences may have an impact later in life with respect to quality of life, suitability and recovery following small intestinal transplantation.

Monitoring of other complications

Central venous access device complications. We suggest checking central venous access device (CVAD) tip position with a chest X-ray to ensure adequate central position with linear growth every 1 or 2 years. A Doppler ultrasound of vessels is helpful to assess patency of vessels when planning a new CVAD insertion.

Neurodevelopmental complications. Multiple comorbidities, including prematurity, long hospitalizations, and multiple septic events, can be associated with impaired neurocognitive outcomes.[15,20] The potential long-term effects of fat minimization on brain development have been also questioned.[1,69] Neurodevelopmental assessments are recommended in these children to identify potential learning and behavioral problems.[15]

Audiology and dental complications. Children with minimal oral intake and a delay in exposure to oral fluids and food are at high risk of dental problems. CVAD infections have been associated with poor dental hygiene and dental infections.[70] An annual dental review is recommended. Children receiving long-term PN are at increased risk of a hearing impairment[69] as a complication of prematurity, exposure to ototoxic medications, or as a result of their underlying disease. Audiology review is recommended annually in young children and then as required.

Quality of life of the children and their families. Data show inconsistent results related to quality of life and overall parental stress and anxiety.[19,71–74] Assessment of quality of life should be an integral part of the management of a child with IF to provide tailored support to families. A validated and adapted questionnaire is available involving children, siblings, and parents.[73]

Vaccination. Children with IF should receive rotavirus vaccine and influenza vaccine in addition to routine immunizations.[75]

Despite consensus that long-term PN requires a thorough monitoring, the rationale behind the frequency of laboratory monitoring is lacking in the literature. A framework of comprehensive monitoring of children on long-term PN is presented in Tables 3 and 4. The frequency of monitoring suggested in these tables is based on our clinical experience and on recommendations from international nutrition societies and relevant articles. The suggested frequency attempts to strike a balance between overmonitoring or unnecessary monitoring and undermonitoring, with the risk of missing deficiencies or toxicities.

Owing to differences in patient characteristics, underlying disease, and comorbidities, a fixed monitoring schedule may "not fit all" patients. The frequency of monitoring outlined in the framework is valid for stable home PN patients with no major complications. For patients with significant IFALD, renal dysfunction, increasing gastrointestinal losses, or those whose PN provision has been modified, the frequency of monitoring may need to be more frequent.

Conclusion

Thorough monitoring of children with chronic IF is a key factor for optimizing long-term outcomes. A practical guide has been developed to assist long-term PN monitoring and standardize practice based on currently available evidence and experience.

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