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Nutrition Support of Children with Chronic Liver Diseases: A Joint Position Paper of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition

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Short title: **Nutrition Support of Children with Chronic Liver Diseases: A Joint NASPGHAN/ESPGHAN Position Paper**

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Abstract:

Chronic liver disease places patients at increased risk of malnutrition that can be challenging to identify clinically and treat. Nutrition support is a key aspect of the management of these patients as it has an impact on their quality of life, morbidity, and mortality. There are significant gaps in the literature regarding the optimal nutrition support for patients with different types of liver diseases and the impact of these interventions on long-term outcomes. This Position Paper summarizes the available literature on the nutritional aspects of the care of patients with chronic liver diseases. Specifically, the challenges associated with the nutritional assessment of these subjects are discussed, and recently investigated approaches to determining the patients' nutritional status are reviewed. Furthermore, the pathophysiology of the malnutrition seen in the context of chronic liver disease is summarized and monitoring, as well as treatment, recommendations are provided. Lastly, suggestions for future research studies are described.

Key words: cirrhosis, malnutrition, metabolic bone disease, nutrient deficiencies, frailty

What is known

- Chronic liver disease is associated with malnutrition, which is an independent predictor of outcomes.
- Careful monitoring to detect and address nutritional deficiencies in the child with chronic liver disease is important.

What is new

- There are significant gaps in the literature that addresses the optimal nutrition support of patients with chronic liver diseases.
- This report proposes the use of a clinical algorithm to standardize the nutritional management of children with end stage liver disease.

Abbreviations:

BCAA: Branched Chain Amino Acids

BUN: Blood urea nitrogen

CT: Computer Tomography

DHA: Docosahexanoid acid

DXA: Dual-energy X-ray Absorptiometry

EFAD: Essential Fatty Acid Deficiency

EPA: Eicosapentanoic Acid

ESLD: End Stage Liver Disease

FAO/WHO/UNU: Food and Agriculture Organization/World Health Organization/United Nations University

INR: International Normalized Ratio

LCT: Long Chain Triglycerides

LTx: Liver Transplantation

MCT: Medium Chain Triglycerides

MUAC: Mid Upper Arm Circumference

MRI: Magnetic Resonance Imaging

NG: Nasogastric

NJ: Nasojejunal

PIVKA: Proteins Induced by Vitamin K Absence

PN: Parenteral Nutrition

PTH: Parathyroid Hormone

RBP: Retinol Binding Protein

REE: Resting Energy Expenditure

SGA: Subjective Global Assessment

TSF: Triceps Skinfolds

VAD: Vitamin A Deficiency

VDD: Vitamin D Deficiency

VED: Vitamin E Deficiency

VKD: Vitamin K Deficiency

Introduction

Childhood is a vulnerable period of development during which significant variations in nutritional needs can be complicated by underlying medical conditions. Malnutrition is a common complication of cholestatic and end-stage liver diseases, which together may increase the morbidity and mortality of individual patients. Initially, the malnutrition experienced by children with cholestasis may be due to maldigestion and malabsorption of nutrients, along with an increased metabolic demand. Later, as the disease progresses to end stage liver disease, the underlying etiology of malnutrition becomes increasingly complex and includes factors such as anorexia, nausea and vomiting, abnormal nutrient metabolism, increased energy expenditure, maldigestion/malabsorption and may also be iatrogenic (Figure 1). In children with chronic cholestatic and/or end-stage liver disease, there is a definitive need to identify nutritional deficiencies early and to initiate nutritional interventions to both optimize appropriate development and prevent further complications. This is particularly critical in children with end-stage liver disease requiring transplantation, as optimized pre-transplant nutrition may hasten post-transplant recovery while simultaneously decreasing complications. Nutrition support should ideally occur using a multifaceted approach, including detailed investigations of dietary intake and nutritional status, personalized dietary prescriptions and ongoing assessments of nutritional status to guide nutritional interventions. The objective of this Position Paper is to summarize the available literature on the topic of nutrition in chronic pediatric liver disease, provide clinicians with guidance regarding the diagnosis and management of the nutritional issues that occur in this context and highlight areas that require further research.

Methods

An outline of the desired content of this Position Paper was developed by the authors, who are members of the Nutrition and Hepatology Committees of the North American and European Societies of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN and ESPGHAN) and was approved by the NASPGHAN and ESPGHAN Councils. Appropriate terms based on this outline, including cholestasis, end stage liver disease, nutrition, nutritional assessment, nutritional status were used to search the literature using Pubmed, Scopus, CINAHL and Embase databases up to December 31, 2018. A complete list of search terms can be found in the supplementary materials. Reviews, case reports and non-English literature were excluded.

Individual authors were responsible for specific sections of the document, with all co-authors reviewing and editing each section in draft form. All recommendations were made based on the available literature; each author initially providing recommendations for their section. These recommendations were modified on further electronic and phone call communication that ultimately led to the final recommendations that were agreed upon by all the authors (100% agreement was reached for all recommendations).

Nutritional Status Assessment

This section will review general considerations for performing a nutritional status assessment on patients with cholestasis and cirrhosis. Disease-specific details regarding the nutritional aspects of care are discussed later in this Position Paper.

History and Physical Examination

A thorough nutritional assessment should start with the patient's medical history as it pertains to the underlying liver disease and associated comorbidities. It is important to determine whether the patient suffers from conditions that may impact enteral intake, such as dental disease or dysphagia. A review of medications may identify side effects that affect intake. Lastly, socioeconomic factors, such as access to food and vitamins or supplements, should be explored, as they may impact on nutritional interventions and/or outcomes.

In terms of anthropometrics, an appropriately measured length (for those < 2 years) or height (for those ≥2 years; http://www.who.int/childgrowth/training/module_b_measuring_growth.pdf) may be more meaningful in assessing nutritional status than weight [1], particularly in the context of ascites, fluid overload and/or organomegaly. Because poor growth (stunting) is suggestive of chronic malnutrition, and the underlying liver disease (e.g. Alagille syndrome) can also affect length/height measurements, other anthropometrics should be used to determine short-term changes in the nutritional status. Mid upper arm circumference (MUAC) and triceps skin folds (TSF) are useful in this context, as they are less likely to be affected by fluid overload or other complications of end-stage liver disease, are sensitive to short-term nutritional status changes and, in addition, provide information regarding the patients' body composition. MUAC is a reflection of both muscle mass and adipose tissue, whereas TSF reflects adiposity. These anthropometrics have been shown to be predictive of growth in children with chronic liver diseases[2]. In addition, MUAC z-score is an independent indicator of pediatric malnutrition [3]. Serial anthropometric measurements are recommended to evaluate the impact and adequacy of nutritional interventions [4]. The frequency of anthropometry depends on severity of malnutrition but can range from every 2 weeks to every 3 months. Beyond isolated anthropometric measurements, combinations of anthropometric changes and symptoms have been used (e.g. in Subjective Global Assessment [SGA]) in adults to classify patients into well nourished, mildly malnourished, moderately malnourished, and severely malnourished. A modified version of the SGA has been validated for use in pediatrics and shown to correlate with infectious complications, as well as hospital length of stay. This has not yet been validated in children with chronic/end-stage liver diseases [5, 6]. Lastly, while a variety of nutritional screening tools have been developed for use in general pediatrics [7], they have not been validated in chronic pediatric liver disease , and as such, there is insufficient evidence to support the use of a particular screening tool in this context.

Patients with chronic liver diseases (particularly those with cholestasis) often have protein, essential fatty acid and fat-soluble vitamin deficiencies. Other nutrients, such as B and C vitamins, carnitine and selenium, are less likely to be affected, unless the patients are severely malnourished due to suboptimal intake or have specific comorbidities that are associated with nutrient losses (e.g. loss of zinc with diarrhea or loss of B vitamins with hemodialysis). Physical examination findings associated with nutritional deficiencies, which should be considered in the differential diagnosis, are summarized in Table 1.

Functional assessment of nutritional status

Beyond static descriptions of anthropometrics and body composition, functional assessments may provide additional information regarding the nutritional status of patients. Handgrip strength is an example of a functional nutritional assessment, as it provides an estimate of muscle function. It can be measured easily at the bedside and its use for the determination of malnutrition is gaining popularity, including among adults with liver disease [8]. Normative data for pediatric handgrip strength exist for children 4 years of age and older; however, its use in pediatric liver disease is limited and needs to be studied further [9-11].

Frailty is another functional assessment that is in large part reflective of nutritional status. Frailty encompasses measures of slowness, weakness, shrinkage, exhaustion and diminished activity. In adults with end stage liver disease, frailty correlates with morbidity and wait-list mortality [12]. In adult patients listed for liver transplantation, frailty is associated with hospital length of stay and need for rehabilitation[13, 14]. Furthermore, frailty is superior to markers of liver disease severity, as an indicator of quality of life in this context[15]. Modified measures of frailty (e.g. frailty index: the combination of handgrip strength, chair stands and balance) along with MELDNa[+] outperform either measure alone in terms of predicting 3-month liver transplant wait list mortality in adults[16]. In pediatrics, frailty is a fairly novel concept. A modified version of frailty for pediatrics (measured using validated tests, such as the 6 minute walk for slowness, TSF for shrinkage, handgrip strength for weakness, PedsQL® questionnaire for exhaustion and a physical activity questionnaire to assess diminished activity) was assessed in a recent multi-center study in children[17]. In this study, frailty could distinguish children with chronic liver disease from those with end-stage liver disease. The utility of pediatric frailty assessment for the prediction of short- and long-term patient outcomes remains to be determined.

Imaging approaches to determine nutritional status

The nutritional status of patients with chronic or end-stage liver disease can also be determined by imaging modalities that assess body composition. The tools most commonly used for this purpose are Dual-energy X-ray Absorptiometry (DXA) and bioelectrical impedance (BIA), though newer modalities, such as air-displacement plethysmography, are becoming increasingly available. These modalities (DXA, BIA) provide a measure of fat and fat-free mass, which are helpful when designing the nutritional rehabilitation approach (e.g. increased calories needed to increase fat mass, whereas an optimized energy-protein ratio, in conjunction with physical activity, is needed to increase fat-free mass). It should be noted that fluid overload decreases the accuracy of these tools [18]. Information regarding fat and muscle mass can also be obtained through Computed Tomography (CT) scans or Magnetic Resonance Imaging (MRI), which are typically obtained for other purposes. Currently, however, the radiation exposure from CT scans, and the associated cost and possible need for sedation associated with MRI scans prevent their routine clinical use in assessing body composition.

Sarcopenia, defined as severe muscle depletion, is a marker of poor nutritional status and is associated with wait-list mortality in adults with end stage liver disease [19]. Sarcopenia is also associated with morbidity (e.g. risk of sepsis, hospital length of stay) and mortality following liver transplantation [20, 21]. Nutrition support in the perioperative period aimed at reversing sarcopenia is associated with improved outcomes [22, 23]. In observational studies of children, imaging-based measurements of psoas muscle surface area have been used to determine the presence of sarcopenia [24, 25]. Limited data suggest that psoas muscle surface area is significantly lower in children with end-stage liver disease compared to healthy controls. This may serve as a complementary assessment of nutritional status, as it does not correlate with commonly used measures, such as weight [24, 25]. Future studies in broader populations of children with liver disease are needed to better understand the utility of measuring sarcopenia as a means of predicting short- and long-term morbidity and mortality.

RECOMMENDATIONS:

1. Beyond weight and height measurements, clinicians should monitor MUAC and TSF serially in patients with chronic liver disease. The frequency of the measurements depends on the nutritional status and can range from every two weeks to every 3 months.
2. A careful, nutrition focused, physical examination is recommended in every clinic visit.

Challenges with Assessing Energy, Macro- and Micronutrient Status and Requirements in Cholestasis and Cirrhosis

The presence of cholestasis and cirrhosis complicates nutritional assessments. The following section highlights the challenges associated with the assessment of energy, macronutrient and certain micronutrient requirements of children with cholestasis or cirrhosis. A practical, expert opinion-based approach to monitoring for nutritional deficiencies is summarized in Table 2.

Energy and macronutrients

a. Energy expenditure

The energy requirements of patients with liver disease depend on their resting energy expenditure (REE), their activity level, as well as the severity of their maldigestion/malabsorption. Determining the caloric requirements of patients with liver diseases is challenging in the clinical setting. The equations typically used to predict REE are inaccurate, particularly in those with end-stage liver disease and correct clinical estimates of the degree of maldigestion/malabsorption are difficult to obtain [26]. The REE of children with cholestasis and cirrhosis may also depend on disease severity [27-29]. When available, indirect calorimetry can be used to measure the REE. When indirect calorimetry is not available, clinicians can start by estimating the REE using the Food and Agriculture Organization/World Health Organization/United Nations University (FAO/WHO/UNU) equation, which has been validated in children [30]. This provides a starting point, which should subsequently be modified based on the progress of the patients' nutritional status.

b. Fat

The fat requirements of patients with chronic/end-stage liver disease depend on their nutritional status, as well as the presence and severity of maldigestion/malabsorption. Typically, patients consume diets with standard amounts of fat, which in children and adolescents provide ~25-30% of total calories. Formulas enriched in medium chain triglycerides (MCT) are often used in cholestatic infants, given the fact that they do not require bile salts for digestion and can enter the enterocytes through passive diffusion. Increased provision of fat is justified in the context of excess fecal fat losses, although the exact amount of additional fat required is patient-specific and depends on the degree of gastrointestinal losses. Serial TSF measurements can assist in determining the need for additional fat supplementation.

Children with cholestasis are at increased risk of essential fatty acid deficiency (EFAD), secondary to fat maldigestion/malabsorption, inefficient elongation of essential fatty acid precursors by dysfunctional hepatocytes and enhanced peroxidation of lipids [31, 32]. EFAD can also be iatrogenic, particularly when diets high in medium chain (MCT) and low in long chain triglycerides are used [33]. EFAD correlates with fat-soluble vitamin deficiencies and should be suspected in this context [34]. Clinical signs of EFAD, such as dry, rough skin, poor growth, numbness, paresthesias and vision impairment may go unrecognized or be misdiagnosed as vitamin deficiencies [35]. Total fatty acid profiles in the red blood cells can be used to test for EFAD. EFAD testing is positive when linoleic acid, α-linolenic acid, eicosapentanoic acid (EPA) and/or docosahexanoic acid (DHA) are below reference ranges for age in patients with either clinical signs of EFAD or severe fat soluble-vitamin deficiencies not improving with supplementation [36]. The classically used triene to tetraene ratio >0.2 is not a sufficient testing approach for EFAD and it provides no information regarding the status of ω-3 fatty acids [36].

c. Protein

Protein requirements in children with chronic and end stage liver disease are typically increased, due to protein loss, increased amino acid oxidation and poor nutritional status. Albumin (half-life of ~20 days), prealbumin (half-life of 2 days), transferrin (half-life 10 days) and retinol-binding protein (half-life 12 hours) may be generally used to assess protein status. In the context of chronic liver disease and inflammation, however, these markers have variable utility, as they tend to be low due to either decreased synthesis or increased losses (in stool, urine or the interstitial space), and hence are not necessarily reflective of nutritional status [37, 38]. Blood urea nitrogen (BUN) is affected by hydration status, as well as the capacity of the liver to make urea. In the absence of dehydration or liver failure (in which case ammonia levels are typically elevated), a low BUN can be used as an indirect marker of suboptimal protein intake. Nitrogen balance studies and serum creatinine levels are also affected by comorbidities seen in end-stage liver disease (e.g. renal impairment) and as such should be interpreted with caution [39]. Other parameters, such as measures of sarcopenia (discussed above), may be more useful indirect indicators of chronic protein intake; however, their utility in this context has not yet been adequately studied.

d. Carbohydrates

Carbohydrate requirements in patients with chronic or end-stage liver disease are also challenging to determine and depend on associated comorbidities. Typically, patients receive ~50-65% of their total calories in the form of carbohydrates. Hyperglycemia secondary to insulin resistance, as well as hypertriglyceridemia (which may also indicate impaired glucose tolerance) may be driven by the underlying liver disease, but may also suggest excess carbohydrate provision. In contrast, patients with cirrhosis or acute liver failure are at risk of hypoglycemia because of limited stores and an inability to mobilize these stores, particularly following prolonged periods of fasting. Vulnerable patients, such as infants younger than 6 months of age, may have asymptomatic hypoglycemia, suggesting that clinicians should have high clinical suspicion for this complication.

Micronutrients

1. Vitamin A

The majority of vitamin A (90%) is stored in the liver and vitamin A content decreases as liver disease progresses [40-42]. Vitamin A status can be assessed using a variety of approaches [40] but in clinical practice, serum retinol and retinol binding protein (RBP) levels are most commonly used. When serum retinol drops below 20 mcg/dL a modified relative dose response test (RDR) can be used to confirm the result [40]. Serum RBP levels are inaccurate in those with advanced liver disease [42]. Beyond serum markers, ophthalmologic assessments have poor sensitivity and specificity to detect vitamin A deficiency (VAD) [40]. However, clinicians should enquire about the sensation of dry eyes or evidence of visual impairment in poorly lit areas and refer cholestatic or malnourished patients with low serum RBP levels or abnormal RDR testing to ophthalmology for further assessment.

2. Vitamin E

Vitamin E deficiency manifests predominantly with neurologic symptoms, which may not be reversible with vitamin E supplementation [43-46]. Vitamin E circulates in lipoproteins and, as a result, cholestasis can be associated with falsely elevated vitamin E levels [47]. The ratio of vitamin E to total lipids (triglycerides, phospholipids and total cholesterol) should be used to screen for vitamin E deficiency (VED) in patients with cholestasis and hyperlipidemia [46-48]. The cut-off for VED is 0.6 mg of serum vitamin E/g of total lipids in those 1-12 years of age and 0.8 mg/g in older children and adults [47]. The serum vitamin E to total cholesterol ratio has also been used to assess for VED [49, 50]; however, it may provide false negative results when screening cholestatic children for VED [51]. Red blood cell acanthocytosis, which can be seen on a blood smear, is another indication of VED.

3. Vitamin K

Vitamin K increases the affinity of certain proteins to calcium. In the clotting cascade, vitamin K activity facilitates the calcium-dependent activation of clotting factors, while in the bones vitamin K enhances calcium deposition. INR is used clinically to assess vitamin K status. However, while the INR reflects vitamin K status in terms of the clotting cascade, it may be an inaccurate reflection of vitamin K status from a bone mineralization perspective [52, 53]. Vitamin K deficiency (VKD) should be considered in the differential diagnosis of metabolic bone disease in cholestatic patients, even in those with a normal INR. Plasma PIVKA-II (protein induced in vitamin K absence) levels may assist in determining vitamin K deficiency; however, this assay is not widely available in the clinical setting [52, 53].

4. Vitamin D

The liver is central to vitamin D metabolism and absorption. Osteopenia and rickets secondary to vitamin D deficiency (VDD) are not uncommon in cholestasis and cirrhosis [54-56]. While cholestasis is associated with lower serum levels of 25-hydroxy vitamin D, non-cholestatic patients are also at risk for VDD, particularly in the context of advanced liver disease [57]. If VDD is suspected, further work-up including measurement of serum parathyroid hormone (PTH), calcium and phosphate levels may be indicated.

5. Zinc

Zinc circulates predominantly bound to albumin and serum zinc levels are used to screen for deficiency, which may be associated with skin rashes and diarrhea [58, 59]. Conditions affecting albumin levels and inflammation may impact serum zinc levels [58]. In children with cirrhosis, serum zinc levels do not correlate with tissue zinc content and, as such, clinicians should have a high index of suspicion and provide zinc supplements to patients with gastrointestinal and dermatologic manifestations suggestive of zinc deficiency [60]. Since zinc is required for alkaline phosphatase synthesis, low alkaline phosphatase levels may be suggestive of zinc deficiency. However, alkaline phosphatase levels should be interpreted with caution in patients with cholestasis and/or bone disease, which cause elevations in this biomarker.

RECOMMENDATIONS:

1. Clinicians should familiarize themselves with the limitations of nutritional biomarkers in the context of chronic liver disease.

Optimal nutrition support: Cholestatic Liver Disease

Pathophysiology of Nutritional Deficiencies in Cholestatic Liver Disease

In addition to the maldigestion and malabsorption seen in cholestasis (Figure 1), affected children also have an increased metabolic rate, similar to those with end stage liver disease (see 'Nutrition in Cirrhosis and Peri-transplant Period' section below) [27, 61]. Amino acids are used for gluconeogenesis, resulting in increased oxidation of branched chain amino acids (BCAA), which occurs even in the context of mild cholestasis [61]. This contributes to progressive muscle wasting, sarcopenia and protein-energy malnutrition. Cholestasis is also associated with fat maldigestion due to the limited delivery of bile acids to the small intestine. This results in excessive intestinal calorie losses. In addition, unabsorbed free fatty acids in patients with cholestasis can bind to dietary calcium, leading to gastrointestinal calcium losses, contributing to metabolic bone disease and oxalate nephrolithiasis. The metabolic bone disease seen in this context is multifactorial and can be due to VDD, other fat-soluble vitamin deficiencies (e.g. vitamin K), physical inactivity, undernutrition and hormonal changes. Oxalate nephrolithiasis occurs secondary to decreased calcium-oxalate binding in stool (resulting from preferential binding of calcium to fatty acids), which leads to increased intestinal oxalate absorption [62].

Dietary plans aimed at supporting patients with cholestasis should take into consideration the altered bioavailability and metabolism of nutrients seen in cholestasis (see Table 2).

Prevalence of Malnutrition and Nutritional Deficiencies in Cholestatic Liver Disease

While few studies report on the nutritional status of cholestatic children, and typically include small cohorts, the prevalence of malnutrition in this population is significant [63]. In a study of 38 infants with neonatal cholestasis, 39% were found to have malnutrition using MUAC measurements [63]. Another study of 91 infants, median age 12 months, revealed that 44 % of children had reduced MUAC, and 64% had reduced TSF thickness. In contrast, only 33% had reductions in weight-for-age measures [64]. A retrospective Brazilian study noted that 64% of cholestatic children were stunted [65]. These data suggest that recognition of malnutrition in liver disease is a crucial first step in providing these patients with optimal care.

Metabolic bone disease in the context of liver disease (hepatic osteodystrophy) is a prevalent comorbidity of cholestatic children and may occur in the first few months of life. Metabolic bone disease should be considered in those with a history of fractures, bone pain, as well as laboratory evidence of low serum 25-OH vitamin D and phosphate levels or elevated parathyroid hormone levels. Elevations in serum levels of alkaline phosphatase may also suggest comorbid metabolic bone disease; however, this biomarker is also elevated in cholestasis. A study of 37 children, ages 2 to 22 months, showed that in spite of normal levels of 25-OH vitamin D, radial bone mineral density approached -3 to -5 standard deviations by 2 years of age [66]. Similarly, a cross-sectional study of 50 children with cholestasis who had bone mineral density, 25-OH vitamin D levels, and serum calcium/ phosphorus levels assessed, revealed that reduced bone density was present in 56% of patients. More than half of these patients had reductions in serum calcium levels, rather than 25-OH vitamin D[67]. The measurement of PIVKA-II in cholestatic children has revealed that VKD significant for bone health can occur even in those with a normal INR (39%) [53]. Lastly, a study of 148 cholestatic children (>5 years of age) with chronic intrahepatic cholestasis, Alagille syndrome, alpha-1 antitrypsin deficiency and bile acid synthetic disorders indicated that patients with chronic intrahepatic cholestasis were at highest risk of metabolic bone disease even after controlling for anthropometrics [68]. Bone deficits generally did not correlate with the severity of cholestasis; however, in patients with Alagille syndrome bone density correlated with their poor nutritional status, as well as the severity of their cholestasis.

Data on specific nutrient deficiencies in children with cholestasis is confounded by the inclusion of patients with co-morbid end-stage liver disease. Assessed independently, children with cholestasis alone may have a higher risk of EFAD, and fat-soluble vitamin deficiencies with the prevalence of these deficiencies dependent on the severity of cholestasis [31]. The prevalence of fat soluble vitamin deficiencies in infants with biliary atresia during the first 6 months post Kasai hepatoportoenterostomy is reported to be 29-36% for VAD, 21-37% for VDD, 10-22% for VKD and 16-18% for VED [69]. In addition, ß-carotene is low in as many as 85% of children with cholestatic liver disease [70]. A study of 27 children with end-stage liver disease, who were consuming nearly 70% of their estimated calorie/protein requirements, also reported iron, zinc and selenium deficiencies in 32%, 42% and 13% patients, respectively [71].

Approach to Nutrition Support in Pediatric Cholestasis

The approach to nutritional supplementation of children with cholestasis should focus on providing increased total calories, lipids, and protein, while avoiding extended periods of fasting (see Table 3). Given the lack of randomized controlled trials, this approach is based on less stringent evidence. Ongoing steatorrhea may result in significant calorie losses the repletion of which requires a significant increase in energy provision over what may be derived from standard energy equations or measured via indirect calorimetry [72]. Sole increases in fat provision in efforts to calorie boost the diet may be inappropriate. Increased protein catabolism must also be addressed through increased protein supplementation, which may be required even in mild-to-moderate cholestasis.

MCTs remain a key component of supplementation in cholestasis. Limited data point to improved growth in cholestatic infants fed with a ratio of MCT/LCT (long chain triglyceride) supplementation of 30% to 70% (MCT/LCT mix). It is important to highlight that MCTs are less efficient fuel sources, as they contain fewer kilocalories per gram than LCTs (8.3 kcal/g MCT vs. 9 kcal/g LCT), increase total energy expenditure, and are not a source of essential fatty acids. For this reason, a diet of exclusive MCT lipids (>80%, or lower in severe cholestasis) increases the risks of EFAD and may contribute to suboptimal weight gain. Supplementation of the diet with MCT may be offered in the form of both MCT oils, and MCT-containing formulas. Dietary sources of MCT include coconut oil, palm oil, and dairy products and can be added to table foods in older children. There is no clear consensus on absolute ratios and concentration of MCT provided, but remaining mindful of EFAD when the MCT provision exceeds >80% of total fat intake is important. Limited availability of essential fatty acids can have a negative impact on growth and brain development[73], even in those who do not have clinically evident EFAD, further underscoring the importance of providing adequate LCT. The amount of LCT that is required to prevent EFAD is 3% of total fat calories in healthy subjects; however, in the context of cholestasis LCT requirements may be much higher, and depend on the severity of the fat maldigestion/malabsorption. Lastly, it should be noted that while the practice of enriching the diet with MCT oils in the clinical setting is commonplace, a trial comparing MCT to LCT supplementation has never been performed in pediatric cholestasis.

Correction of fat-soluble vitamin deficiencies can be challenging, and obtaining fat-soluble vitamin supplements that are modified to enhance their absorption under conditions of fat malabsorption are frequently complicated by global product shortages. Moreover, while medically necessary, these supplements are often not covered by insurance providers in some countries, leaving families with high out-of-pocket expenses. Initial supplementation is most commonly delivered through water-soluble ADEK multivitamin formulations. These aqueous preparations can be transported directly into the portal circulation without the need for bile salts[69, 74]. Individual vitamin preparations are commonly required to meet requirements. For example, alpha-tocopherol polyethylene glycol 1000 succinate (TPGS) is a tocopherol (vitamin E) isomer that exhibits improved systemic absorption due to its amphipathic molecular structure. This compound forms micelles without the need for bile salts, thus supporting its transport across the intestinal epithelium and into the portal circulation independently [75]. In addition, it facilitates the absorption of other fat soluble vitamins (vitamin D) [76]. Vitamin A supplementation requires close monitoring, as hypervitaminosis A can cause hepatic fibrosis and worsening liver disease [40, 77]. Vitamin D should be provided as cholecalciferol (D3) due to its greater bioavailability and affinity for vitamin D-binding protein than ergocalciferol (D2). There is no consensus on upper limits of serum levels, but serum levels of 25-OH Vitamin D >20 nmol/L should be achieved [78].

To conclude, the assessment of nutritional status in cholestatic children should include MUAC, TSF, and height-for-age measurements, in addition to weight-for-age. Protein-energy malnutrition is common in pediatric liver disease and should be managed in conjunction with a nutrition support team where available. This approach optimizes anticipatory monitoring, proactive supplementation and ongoing follow-up, as summarized in Table 3. Prolonged periods of fasting should be avoided. There is no consensus on the optimal ratio of MCT/LCT supplementation but MCT dosing should be limited to <80% of total fat energy intake to prevent EFAD and enhance weight gain.

RECOMMENDATIONS:

1. Nutrition support of cholestatic infants should be optimized to prevent and treat nutritional deficiencies. A detailed approach to optimizing nutrition support is provided in Table 3.

Optimal nutrition support: Nutrition in Cirrhosis and the Peri-transplant Period

The most common indications for pediatric liver transplantation (LTx) are end-stage liver disease (due to conditions such as biliary atresia, alpha-1 antitrypsin deficiency, Alagille syndrome, and autoimmune hepatitis) or acute liver failure resulting from toxic, infectious, metabolic or idiopathic causes [79-81]. Particularly in end-stage liver disease, nutritional status can affect morbidity and mortality in both the peri-transplant period, as well as long-term following LTx [82-85].

Pathophysiology of Nutritional Deficiencies in Cirrhosis.

Malnutrition in LTx candidates refers not only to compromised nutritional status (including sarcopenia) and metabolic bone disease, but also to complications such as nutrition-related cardiomyopathy [82, 85]. Beyond the pathophysiology discussed in the cholestasis section and summarized in Figure 1, patients with end stage liver disease also develop insulin resistance [86], which fuels a catabolic state that may further worsen their nutritional status. In terms of fat metabolism, the decreased respiratory quotient of children with end-stage liver disease undergoing indirect calorimetry suggests active lipid oxidation, which is seen in both the fed and fasted states [27]. Total energy expenditure is also increased in cirrhosis (sometimes in excess of 150% of expected) rendering it challenging to meet energy requirements [83, 85] particularly in the context of organomegaly, ascites (necessitating fluid restriction) and anorexia.

Prevalence of Malnutrition and Nutritional Deficiencies in Cirrhosis

The worldwide prevalence of malnutrition in infants and children with end stage cholestatic liver disease is significant. In a longitudinal study from Australia, the mean height/length z-score at the time of liver transplant was -1.12±1.50 (n=32; median age 2.1 years, range 0.4-10.9) [87]. A Chinese study revealed growth impairment in 69% of children listed for transplantation (n=51; mean age 3.7 years, range 1.1-13.0) [88]. Recent data from the United States (n=35) indicate that children with end-stage liver disease have on average a 23% reduction in muscle mass, but a 69% increase in visceral and a 29% increase in subcutaneous fat compared to healthy controls [25].

Approach to Nutritional Support of Children with Cirrhosis

The approach to the nutritional support of children with cirrhosis is based on limited evidence due to the paucity of randomized controlled trials. It is well known that better pre-transplant nutritional status is associated with better post-transplant outcomes [89-91]. However, only a single small randomized controlled trial focused on nutritional intervention in pediatric patients awaiting LTx exists. This study showed that delivering branched-chain amino acid (BCAA)-enriched, semi-elemental formulas to young children (median age 1.25 years) by nasogastric tube can lead to improved anthropometric outcomes compared to a standard semi-elemental formulation [92]. A Cochrane review failed to identify the benefits of nutritional interventions for adult LTx patients, but provided weak evidence that, compared with standard dietary advice, adding a nutritional supplement to the usual diet of patients listed for LTx may have a beneficial effect on clinical outcomes after LTx [93]. Considering the differences in the pathophysiology and comorbidities of adult and children with cirrhosis, pediatric-specific literature is needed.

A practical approach to the nutrition support of patients with end stage liver disease is shown in Figure 2. In terms of macronutrient composition, patients with ESLD should receive ~40% of total energy in the form of fat (this varies depending on the severity of cholestasis) and 40-60% in the form of carbohydrates (balancing the hypoglycemia from ESLD and hyperglycemia from insulin resistance). Low protein diets should be avoided (except when severe encephalopathy is present and in that context protein restriction should not exceed 2-3 days) [83]. While the protein requirements of children with ESLD are not known, adult data suggest that adequate protein intake attenuates the muscle catabolism seen in cirrhosis, without exerting a negative impact on recovery from hepatic encephalopathy[94, 95]. Based on the adult literature, a patient's protein requirements should be met and protein intake should not be decreased with the sole purpose of addressing rising ammonia levels. Mineral and trace elements deficiencies should be monitored and age-appropriate single/multivitamin products used as supplementation, as needed [83]. The optimal frequency of monitoring has not been established. Under certain circumstances, such as in patients listed for combined liver-kidney transplantation or those inborn errors of metabolism requiring liver transplant, determining the optimal nutritional approach may be even more complex [96].

The overall diet of patients awaiting LTx is theoretically similar to age-appropriate healthy children. However, more frequent feeding (every 1-2 hours in infants and 3-4 hours in older children) or nighttime feeding may be needed to prevent consequences resulting from above-mentioned impaired glucose and protein metabolism. Persistent hypoglycemia may require continuous feeding via a nasogastric or nasojejunal tube (including at nighttime) or total parenteral nutrition in severe refractory cases. In adults with cirrhosis, the provision of a bedtime snack or overnight feeding to prevent prolonged fasting (>8 hours) not only attenuates the risk of complications, such as hypoglycemia, but may also improve the patients' nutritional status[97, 98]. In infants, breast milk can be supplemented with a breast milk fortifier [85]. If breast-milk is not available, a MCT-rich infant formula should be used. Another option to enhance the caloric needs of infants listed for transplantation is to increase the caloric density of formula to 0.8-1 kcal/mL (24-30 kcal/oz) [85]. Pre-made high calorie (1 kcal/ml; 30 kcal/oz) formulas can be also considered but they usually do not contain MCT. Modular supplements (MCT or LCT oils, carbohydrate or protein powders) can also be added to infant formula to reach the desired calorie concentration (typically does not surpass 1 kcal/mL in infancy).

In older children, specific dietary prescriptions depend on their underlying liver disease, nutritional status, and the identified macro/micronutrient deficiencies [83]. In cases of early satiety or volume/fluid restriction, small but more frequent meals of increased caloric density may be needed [83]. If appropriate macro-/micronutrient intake cannot be achieved by changes in regular diet, modular supplements (carbohydrate-based powders, protein powders, MCT oils etc.) and/or enteral formulas can be used. In patients who are unable to consume adequate nutrition orally for appropriate growth, nasogastric (or nasojejunal) feeding is required. The insertion of a percutaneous gastrostomy carries significant risk in patients with portal hypertension and should be avoided [99, 100]. Failure to achieve adequate nutrition and growth using enteral feeds should prompt use of parenteral nutrition (PN) [82, 83, 85]. In a small retrospective study, PN improved the nutritional status (MUAC, TSF) of malnourished patients with biliary atresia listed for transplantation, compared to patients not receiving PN [84]. Improved anthropometrics at transplantation were associated with favourable outcomes post transplant [84]. It should be noted, however, that PN use can contribute to fluid and sodium overload, has previously been associated with worsening ascites and increased risk of gastrointestinal bleeding, [84] and may increase the risk of central line associated blood stream infections. Finding an optimal feeding plan can be challenging and time consuming, but it is crucial, as failure to do so can adversely affect not only the global health of patients, but also their quality of life and family functioning [82]. A practical approach to the nutritional support of children with end-stage liver disease is included in **Figure 2** [101]. This suggested approach is based on expert opinion and should be modified based on the patients' clinical status, assessment and progression.

RECOMMENDATIONS:

1. Nutritional status, growth and eating habits should be closely monitored. The frequency of monitoring depends on the severity of malnutrition and severity of liver disease and can range from every 2 weeks to every 3 months.
2. Increased feeding frequency, increased calorie density of consumed foods and use of modular supplements should be used as needed.
3. Nasogastric/nasojejunal feeding should be considered, when appropriate.
4. Parenteral nutrition can be used when enteral nutrition (oral, gastric and jejunal) is not tolerated or fails to achieve growth targets.

Approach to the Nutrition Support of Children Following Liver Transplantation

Literature on the nutritional management of pediatric LTx recipients is limited. A randomized control trial of 24 patients, mainly adults (ages 16-62 years)[102] showed that enteral feeding can be safely introduced early in the post-operative period. In this study, 14 patients received NJ feeds within the first 18 hours post LTx and 10 patients were started on PN. By post-operative day 10, both groups had similar oral intake and anthropometric measurements, suggesting the feasibility of introducing early enteral feeding post-LTx. There are no pediatric studies comparing early enteral vs. parenteral nutrition and their impact on morbidity, mortality and overall outcome after LTx. In addition, it is unclear whether a certain approach to feeding (e.g. NG vs. oral vs. NJ) or diet (e.g. concentrated vs. regular strength formulas) is superior in the post LTx period. While oral intake is encouraged, young

LTx recipients may have oromotor delays impacting their ability to feed due to pre-LTx comorbidities. From a physiological perspective, provided that there are no biliary complications, there is no reason to use high MCT products post LTx.

Immunosuppressive and other supportive medications (e.g. loop diuretics or antifungals) may contribute to specific electrolyte disturbances, which need to be monitored closely and treated accordingly. For example, immunosuppressive therapy with tacrolimus can lead to hyperkalemia or hypomagnesemia. Dietary adjustments or provision of supplements is typically sufficient to manage these laboratory abnormalities.

Nutritional Outcomes Post Liver Transplantation

Linear growth improves after LTx, yet catch-up growth is greatly impacted by pre- and post-LTx factors. A multicenter study of 892 children who survived beyond the first year post-LTx showed that transplant recipients are shorter that expected based on mid-parental heights [103]. Independent factors associated with shorter stature were pre-transplant linear growth impairment, metabolic disease as an indication for LTx, re-transplants and long-term use of corticosteroids post-LTx.

Apart from undernutrition, obesity also affects LTx recipients. Based upon a United Network for Organ Sharing (UNOS) data analysis, approximately 15 % of children are obese at the time of LTx [104]. This issue places LTx recipients at risk of obesity-related comorbidities such as diabetes mellitus, cardiovascular disease, hyperlipidemia and hypertension. In addition, 26% of pediatric LTx recipients are overweight or obese at a median time of 6 years post LTx and many have co-existent cardiometabolic risk factors, including hypertension (44%), hypertriglyceridemia (39%), insulin resistance (27%), low HDL (20%), and central obesity (19%) [105]. In this study, 19% had 3 or more co-existing cardiometabolic risk factors, which is almost five fold higher than that of the general population. LTx children are predisposed to these comorbidities predominantly due to the side effects of immunosuppressive therapy used to prevent rejection; however other factors, such as indication for LTx may also play a role. The strongest predictor of post-LTx overweight status is weight at the time of LTx. Other factors that predict post-LTx obesity are Hispanic ethnicity and steroid use at follow-up [106]. Interestingly, the prevalence of obesity decreases from 19% and 18% at 1 and 3 years post LTx, respectively, to 11% at 5 years [106]. Obesity and metabolic syndrome are concerning features as they are associated with increased risk of graft loss, overall morbidity and mortality [107, 108].

Bone disease is a common comorbidity of pediatric LTx recipients. It typically arises in the pre-LTx period due to complications of end-stage liver disease, such as fat-soluble vitamin maldigestion, use of loop diuretics and overall deconditioning [109, 110]. Following LTx, other factors, such as corticosteroid use, can further impair bone health. Studies assessing the bone mineral density of LTx recipients at various time-points post-transplant have revealed bone deficits in 0-7% of patients [111-113]. Results of a retrospective study of 199 pediatric LTx recipients showed that 53% had vitamin D levels below 20 ng/mL 6 years post LTx and 14% had levels below 12 ng/mL [114]. The main factors associated with VDD were season at the time of testing, corticosteroid use and ethnicity. The prevalence of VDD was highest early on post transplant (33% at 1 year post LTx vs. 12% later than 1 year post LTx). Given these data, monitoring of vitamin D levels is recommended, particularly in those who had VDD and/or established bone disease pre-LTx. Vitamin D levels should be monitored periodically in the first 2 years post LTx or until normal bone density is achieved [109, 110]. The frequency of this assessment should be determined based on the severity of VDD and/or metabolic bone disease; however, it should occur at minimum every 3-6 months for laboratory investigations. There are no data to support a formal recommendation regarding the need for and optimal frequency of bone mineral density assessments. If obtained, DXA scans should not be performed more often than on an annual basis. Repeat scans are not needed for patients with normal baseline assessments and lack of biochemical evidence of metabolic bone disease. It is also important to monitor micronutrients, such as calcium, magnesium and phosphorus, the homeostasis of which is affected by medications used in the post transplant period, placing patients at risk of bone disease. The need for calcium supplementation should be assessed in patients requiring vitamin D supplementation and in those with evidence of decreased bone density.

RECOMMENDATIONS

1. A formal assessment of nutritional status is recommended for all children before and after liver transplantation, the frequency of which depends on the nutritional status and can range from every 2 weeks to every 3 months and should occur until adequate growth patterns (achieve at minimum BMI>-1 SD and/or MUAC>-1 SD without deceleration in weight for length z-score) are established post-LTx.
2. Nutritional interventions (provision of appropriate calories to achieve MUAC and TSF>10^{th} percentile for age, correction of micronutrient deficiencies) to optimize nutritional status in the peri-transplant period should be implemented, as they are associated with improved patient outcomes.
3. Liver transplant recipients should be screened for overweight/obesity and hypertension at every routine medical encounter. Patients should also be tested for other metabolic syndrome-related complications, such as dyslipidemia and insulin resistance at minimum annually.
4. Monitoring of bone health is advised in liver transplant recipients, particularly in the first 2 years post LTx. Monitoring with laboratory investigations should occur every 3-6 months.

Recommended topics for future research

Based on the aforementioned gaps in the literature, we recommend the following topics as future research areas:

1. Determine the utility of functional assessments of nutritional status (e.g. frailty) on:
    a. Guiding the approach to nutrition support (assessing the impact of nutritional interventions on nutritional status)
    b. Predicting long-term outcomes
2. Determine the optimal nutrition support for patients across the spectrum of liver disease severity:
    a. Protein requirement
    b. Optimal ratio of macronutrient provision (calories from fat vs. protein vs. carbohydrates)
    c. Optimal use of MCT oil
    d. Optimal timing and approach to aggressive nutritional rehabilitation with nasogastric/nasojejunal tubes and PN.
3. Determine the nutritional risk of liver transplant recipients and the optimal approach to monitoring and intervening.

Conclusions

A focus on growth and development is the cornerstone of pediatric care. Malnutrition is a common complication of cholestasis and cirrhosis. This has the potential to increase morbidity and mortality of individual patients and occurs as a result of multiple overlapping factors, including anorexia, abnormal nutrient metabolism, increased energy expenditure, and malabsorption. Optimizing the nutritional status of children affected by liver disease by ensuring adequate calorie, protein, fat and micronutrient provision, has the potential to positively impact survival, but also improve development, quality of life and overall health. Optimal nutritional assessments are multifaceted and must include dietary intake, careful physical exam, anthropometric measurements, functional assessments and attention to both micro and macronutrient deficiencies. Interventions range from avoidance of prolonged periods of fasting and use of modular supplements (e.g. MCT oil supplementation) to more aggressive nutritional support with nasogastric feeds or total parenteral nutrition. Supplementation of micronutrient deficiencies, including fat-soluble vitamins, may prevent further complications of disease. Repeated assessments of growth and nutrition, at a minimum of every 3 months, allow the clinician to further adjust support according to changing needs over time. For children who progress to end stage liver disease, optimizing nutrition may impact their post- liver transplant course. In the future, carefully designed research may help our practice community further improve the health of children with liver disease by validating comprehensive assessment tools, determining ideal monitoring and supplementation practices and evaluating the risk/benefit of aggressive nutritional interventions, such as the use total parental nutrition.

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References:

1. Mascarenhas MR, Zemel B, Stallings VA. Nutritional assessment in pediatrics. Nutrition 1998;14:105-15.

2. Hurtado-Lopez EF, Vasquez-Garibay EM, Trujillo X, et al. Body Composition Predicts Growth in Infants and Toddlers With Chronic Liver Disease. J Pediatr Gastroenterol Nutr 2017;65:e117-9.

3. Stephens K, Escobar A, Jennison EN, et al. Evaluating Mid-Upper Arm Circumference Z-Score as a Determinant of Nutrition Status. Nutr Clin Pract 2018;33:124-32.

4. Zamberlan P, Leone C, Tannuri U, et al. Nutritional risk and anthropometric evaluation in pediatric liver transplantation. Clinics (Sao Paulo) 2012;67:1387-92.

5. Secker DJ, Jeejeebhoy KN. How to perform Subjective Global Nutritional assessment in children. J Acad Nutr Diet 2012;112:424-31 e6.

6. Secker DJ, Jeejeebhoy KN. Subjective Global Nutritional Assessment for children. Am J Clin Nutr 2007;85:1083-9.

7. Joosten KF, Hulst JM. Nutritional screening tools for hospitalized children: methodological considerations. Clin Nutr 2014;33:1-5.

8. Sharma P, Rauf A, Matin A, et al. Handgrip Strength as an Important Bed Side Tool to Assess Malnutrition in Patient with Liver Disease. J Clin Exp Hepatol 2017;7:16-22.

9. Hager-Ross C, Rosblad B. Norms for grip strength in children aged 4-16 years. Acta Paediatr 2002;91:617-25.

10. Ploegmakers JJ, Hepping AM, Geertzen JH, et al. Grip strength is strongly associated with height, weight and gender in childhood: a cross sectional study of 2241 children and adolescents providing reference values. J Physiother 2013;59:255-61.

11. Molenaar HM, Selles RW, Zuidam JM, et al. Growth diagrams for grip strength in children. Clin Orthop Relat Res 2010;468:217-23.

12. Lai JC, Feng S, Terrault NA, et al. Frailty predicts waitlist mortality in liver transplant candidates. Am J Transplant 2014;14:1870-9.

13. Sinclair M, Poltavskiy E, Dodge JL, et al. Frailty is independently associated with increased hospitalisation days in patients on the liver transplant waitlist. World J Gastroenterol 2017;23:899-905.

14. Tapper EB, Finkelstein D, Mittleman MA, et al. Standard assessments of frailty are validated predictors of mortality in hospitalized patients with cirrhosis. Hepatology 2015;62:584-90.

15. Derck JE, Thelen AE, Cron DC, et al. Quality of life in liver transplant candidates: frailty is a better indicator than severity of liver disease. Transplantation 2015;99:340-4.

16. Lai JC, Covinsky KE, Dodge JL, et al. Development of a novel frailty index to predict mortality in patients with end-stage liver disease. Hepatology 2017;66:564-74.

17. Lurz E, Quammie C, Englesbe M, et al. Frailty in Children with Liver Disease: A Prospective Multicenter Study. J Pediatr 2018;194:109-115 e4.

18. Mouzaki M, Ng V, Kamath BM, et al. Enteral energy and macronutrients in end-stage liver disease. JPEN J Parenter Enteral Nutr 2014;38:673-81.

19. Carey EJ, Lai JC, Wang CW, et al. A multicenter study to define sarcopenia in patients with end-stage liver disease. Liver Transpl 2017;23:625-33.

20. Englesbe MJ, Patel SP, He K, et al. Sarcopenia and mortality after liver transplantation. J Am Coll Surg 2010;211:271-8.

21. Kalafateli M, Mantzoukis K, Choi Yau Y, et al. Malnutrition and sarcopenia predict post-liver transplantation outcomes independently of the Model for End-stage Liver Disease score. J Cachexia Sarcopenia Muscle 2017;8:113-21.

22. Kaido T, Ogawa K, Fujimoto Y, et al. Impact of sarcopenia on survival in patients undergoing living donor liver transplantation. Am J Transplant 2013;13:1549-56.

23. Masuda T, Shirabe K, Ikegami T, et al. Sarcopenia is a prognostic factor in living donor liver transplantation. Liver Transpl 2014;20:401-7.

24. Lurz E, Patel H, Frimpong RG, et al. Sarcopenia in Children With End-Stage Liver Disease. J Pediatr Gastroenterol Nutr 2018;66:222-6.

25. Mangus RS, Bush WJ, Miller C, et al. Severe Sarcopenia and Increased Fat Stores in Pediatric Patients With Liver, Kidney, or Intestine Failure. J Pediatr Gastroenterol Nutr 2017;65:579-83.

26. Carpenter A, Ng VL, Chapman K, et al. Predictive Equations Are Inaccurate in the Estimation of the Resting Energy Expenditure of Children With End-Stage Liver Disease. JPEN J Parenter Enteral Nutr 2017;41:507-11.

27. Greer R, Lehnert M, Lewindon P, et al. Body composition and components of energy expenditure in children with end-stage liver disease. J Pediatr Gastroenterol Nutr 2003;36:358-63.

28. Rovner AJ, Stallings VA, Piccoli DA, et al. Resting energy expenditure is not increased in prepubertal children with Alagille syndrome. J Pediatr 2006;148:680-2.

29. Wasserman D, Zemel BS, Mulberg AE, et al. Growth, nutritional status, body composition, and energy expenditure in prepubertal children with Alagille syndrome. J Pediatr 1999;134:172-7.

30. Energy and protein requirements. Report of a joint FAO/WHO/UNU Expert Consultation. World Health Organ Tech Rep Ser 1985;724:1-206.

31. Socha P, Koletzko B, Pawlowska J, et al. Essential fatty acid status in children with cholestasis, in relation to serum bilirubin concentration. J Pediatr 1997;131:700-6.

32. Socha P, Koletzko B, Swiatkowska E, et al. Essential fatty acid metabolism in infants with cholestasis. Acta Paediatr 1998;87:278-83.

33. Pettei MJ, Daftary S, Levine JJ. Essential fatty acid deficiency associated with the use of a medium-chain-triglyceride infant formula in pediatric hepatobiliary disease. Am J Clin Nutr 1991;53:1217-21.

34. Abdel-Ghaffar YT, Amin E, Abdel-Rasheed M, et al. Essential fatty acid status in infants and children with chronic liver disease. East Mediterr Health J 2003;9:61-9.

35. Holman RT. The slow discovery of the importance of omega 3 essential fatty acids in human health. J Nutr 1998;128:427S-33S.

36. Pavlovski CJ. Screening for essential fatty acid deficiency in at risk infants. Med Hypotheses 2009;73:910-6.

37. Klein S. The myth of serum albumin as a measure of nutritional status. Gastroenterology 1990;99:1845-6.

38. Bettler J, Roberts KE. Nutrition assessment of the critically ill child. AACN Clin Issues 2000;11:498-506.

39. Taylor RM, Dhawan A. Assessing nutritional status in children with chronic liver disease. J Gastroenterol Hepatology 2005;20:1817-24.

40. Feranchak AP, Gralla J, King R, et al. Comparison of indices of vitamin A status in children with chronic liver disease. Hepatology 2005;42:782-92.

41. Peres WAF, Chaves GV, Gonçalves JCS, et al. Vitamin A deficiency in patients with hepatitis C virus-related chronic liver disease. Br J Nutr 2011;106:1724-31.

42. Chaves GV, Peres WA, Goncalves JC, et al. Vitamin A and retinol-binding protein deficiency among chronic liver disease patients. Nutrition 2015;31:664-8.

43. Sokol RJ, Guggenheim MA, Heubi JE, et al. Frequency and clinical progression of the vitamin E deficiency neurologic disorder in children with prolonged neonatal cholestasis. Am J Dis Child 1985;139:1211-5.

44. Landrieu P, Selva J, Alvarez F, et al. Peripheral nerve involvement in children with chronic cholestasis and vitamin E deficiency. A clinical, electrophysiological and morphological study. Neuropediatrics 1985;16:194-201.

45. Alvarez F, Landrieu P, Feo C, et al. Vitamin E deficiency is responsible for neurologic abnormalities in cholestatic children. J Pediatr 1985;107:422-5.

46. Sokol RJ, Butler-Simon N, Heubi JE, et al. Vitamin E deficiency neuropathy in children with fat malabsorption. Studies in cystic fibrosis and chronic cholestasis. Ann N Y Acad Sci 1989;570:156-69.

47. Sokol RJ. Assessing vitamin E status in childhood cholestasis. J Pediatr Gastroenterol Nutr 1987;6:10-3.

48. Sokol RJ. Vitamin E status in cholestasis. J Pediatr 1988;112:324-5.

49. Roda J, Rocha P, Nobre S, et al. Vitamin E deficiency in children with chronic liver disease. Journal of Pediatric Gastroenterology and Nutrition 2016;62:772.

50. Ford L, Farr J, Morris P, et al. The value of measuring serum cholesterol-adjusted vitamin E in routine practice. Ann Clin Biochem 2006;43:130-4.

51. Sokol RJ, Heubi JE, Iannaccone ST, et al. Vitamin E deficiency with normal serum vitamin E concentrations in children with chronic cholestasis. N Engl J Med 1984;310:1209-12.

52. Mager DR, McGee PL, Furuya KN, et al. Prevalence of vitamin K deficiency in children with mild to moderate chronic liver disease. J Pediatr Gastroenterol Nutr 2006;42:71-6.

53. Strople J, Lovell G, Heubi J. Prevalence of subclinical vitamin K deficiency in cholestatic liver disease. J Pediatr Gastroenterol Nutr 2009;49:78-84.

54. Chongsrisawat V, Ruttanamongkol P, Chaiwatanarat T, et al. Bone density and 25-hydroxyvitamin D level in extrahepatic biliary atresia. Pediatr Surg Int 2001;17:604-8.

55. Heubi JE, Hollis BW, Tsang RC. Bone disease in chronic childhood cholestasis. II. Better absorption of 25-OH vitamin D than vitamin D in extrahepatic biliary atresia. Pediatr Res 1990;27:26-31.

56. Sokol RJ, Farrell MK, Heubi JE, et al. Comparison of vitamin E and 25-hydroxyvitamin D absorption during childhood cholestasis. J Pediatr 1983;103:712-7.

57. Fisher L, Fisher A. Vitamin D and parathyroid hormone in outpatients with noncholestatic chronic liver disease. Clin Gastroenterol Hepatol 2007;5:513-20.

58. Karakochuk CD, Barr SI, Boy E, et al. The effect of inflammation on serum zinc concentrations and the prevalence estimates of population-level zinc status among Congolese children aged 6-59 months. Eur J Clin Nutr 2017.

59. Gibson RS, Hess SY, Hotz C, et al. Indicators of zinc status at the population level: a review of the evidence. Br J Nutr 2008;99 Suppl 3:S14-23.

60. Goksu N, Ozsoylu S. Hepatic and serum levels of zinc, copper, and magnesium in childhood cirrhosis. J Pediatr Gastroenterol Nutr 1986;5:459-62.

61. Mager DR, Wykes LJ, Roberts EA, et al. Mild-to-moderate chronic cholestatic liver disease increases leucine oxidation in children. J Nutr 2006;136:965-70.

62. Dobbins JW, Binder HJ. Effect of bile salts and fatty acids on the colonic absorption of oxalate. Gastroenterology 1976;70:1096-100.

63. Yuksekkaya HA, Cakir M, Tumgor G, et al. Nutritional status of infants with neonatal cholestasis. Dig Dis Sci 2008;53:803-8.

64. da Silva FV, Ferri PM, Nascentes Queiroz TC, et al. Nutritional evaluation of children with chronic cholestatic disease. J Pediatr (Rio J) 2016;92:197-205.

65. Mattar RH, Azevedo RA, Speridiao PG, et al. [Nutritional status and intestinal iron absorption in children with chronic hepatic disease with and without cholestasis]. J Pediatr (Rio J) 2005;81:317-24.

66. Argao EA, Specker BL, Heubi JE. Bone mineral content in infants and children with chronic cholestatic liver disease. Pediatrics 1993;91:1151-4.

67. Samra NM, Emad El Abrak S, El Dash HH, et al. Evaluation of vitamin D status bone mineral density and dental health in children with cholestasis. Clin Res Hepatol Gastroenterol 2018;42:368-77.

68. Loomes KM, Spino C, Goodrich NP, et al. Bone Density in Children With Chronic Liver Disease Correlates With Growth and Cholestasis. Hepatology 2019;69:245-57.

69. Shneider BL, Magee JC, Bezerra JA, et al. Efficacy of fat-soluble vitamin supplementation in infants with biliary atresia. Pediatrics 2012;130:e607-14.

70. Socha P, Skorupa E, Pawlowska J, et al. beta-Carotene deficiency in cholestatic liver disease of childhood is caused by beta-carotene malabsorption. J Pediatr Gastroenterol Nutr 2010;51:106-9.

71. Chin SE, Shepherd RW, Thomas BJ, et al. The nature of malnutrition in children with end-stage liver disease awaiting orthotopic liver transplantation. Am J Clin Nutr 1992;56:164-8.

72. Young S, Kwarta E, Azzam R, et al. Nutrition assessment and support in children with end-stage liver disease. Nutr Clin Pract 2013;28:317-29.

73. Uauy R, Calderon F, Mena P. Essential fatty acids in somatic growth and brain development. World Rev Nutr Diet 2001;89:134-60.

74. Shen YM, Wu JF, Hsu HY, et al. Oral absorbable fat-soluble vitamin formulation in pediatric patients with cholestasis. J Pediatr Gastroenterol Nutr 2012;55:587-91.

75. Sokol RJ, Butler-Simon N, Conner C, et al. Multicenter trial of d-alpha-tocopheryl polyethylene glycol 1000 succinate for treatment of vitamin E deficiency in children with chronic cholestasis. Gastroenterology 1993;104:1727-35.

76. Argao EA, Heubi JE, Hollis BW, et al. d-Alpha-tocopheryl polyethylene glycol-1000 succinate enhances the absorption of vitamin D in chronic cholestatic liver disease of infancy and childhood. Pediatr Res 1992;31:146-50.

77. Amedee-Manesme O, Furr HC, Alvarez F, et al. Biochemical indicators of vitamin A depletion in children with cholestasis. Hepatology 1985;5:1143-8.

78. Rosen CJ, Abrams SA, Aloia JF, et al. IOM committee members respond to Endocrine Society vitamin D guideline. J Clin Endocrinol Metab 2012;97:1146-52.

79. Jain V, Dhawan A. Prognostic modeling in pediatric acute liver failure. Liver Transpl 2016;22:1418-30.

80. Pfister ED, McLin VA, Hierro L, et al. "Current state and prospects in managing liver transplanted children". Clin Res Hepatol Gastroenterol 2015;39:292-5.

81. Rawal N, Yazigi N. Pediatric Liver Transplantation. Pediatr Clin North Am 2017;64:677-84.

82. Anthony SJ, Annunziato RA, Fairey E, et al. Waiting for transplant: physical, psychosocial, and nutritional status considerations for pediatric candidates and implications for care. Pediatr Transplant 2014;18:423-34.

83. Leon CD, Lerret SM. Role of Nutrition and Feeding for the Chronically Ill Pediatric Liver Patient Awaiting Liver Transplant. Gastroenterol Nurs 2017;40:109-16.

84. Sullivan JS, Sundaram SS, Pan Z, et al. Parenteral nutrition supplementation in biliary atresia patients listed for liver transplantation. Liver Transpl 2012;18:120-8.

85. Sundaram SS, Mack CL, Feldman AG, et al. Biliary atresia: Indications and timing of liver transplantation and optimization of pretransplant care. Liver Transpl 2017;23:96-109.

86. Mager DR, Wykes LJ, Ball RO, et al. Branched-chain amino acid requirements in school-aged children determined by indicator amino acid oxidation (IAAO). J Nutr 2003;133:3540-5.

87. Ee LC, Hill RJ, Beale K, et al. Long-term effect of childhood liver transplantation on body cell mass. Liver Transpl 2014;20:922-9.

88. Zhang B, Xia Q, Jiang L, et al. [A survey on underweight and growth retardation of 51 children before and after liver transplantation]. Zhonghua Er Ke Za Zhi 2014;52:575-8.

89. Figueiredo F, Dickson ER, Pasha T, et al. Impact of nutritional status on outcomes after liver transplantation. Transplantation 2000;70:1347-52.

90. DiMartini A, Cruz RJ, Jr., Dew MA, et al. Muscle mass predicts outcomes following liver transplantation. Liver Transpl 2013;19:1172-80.

91. Hamaguchi Y, Kaido T, Okumura S, et al. Proposal of Muscle-MELD Score, Including Muscularity, for Prediction of Mortality After Living Donor Liver Transplantation. Transplantation 2016;100:2416-23.

92. Chin SE, Shepherd RW, Thomas BJ, et al. Nutritional support in children with end-stage liver disease: a randomized crossover trial of a branched-chain amino acid supplement. Am J Clin Nutr 1992;56:158-63.

93. Langer G, Grossmann K, Fleischer S, et al. Nutritional interventions for liver-transplanted patients. Cochrane Database Syst Rev 2012:CD007605.

94. Cordoba J, Lopez-Hellin J, Planas M, et al. Normal protein diet for episodic hepatic encephalopathy: results of a randomized study. J Hepatol 2004;41:38-43.

95. Mullen KD, Dasarathy S. Protein restriction in hepatic encephalopathy: necessary evil or illogical dogma? J Hepatol 2004;41:147-8.

96. Bacchetta J, Mekahli D, Rivet C, et al. Pediatric combined liver-kidney transplantation: a 2015 update. Curr Opin Organ Transplant 2015;20:543-9.

97. Chang WK, Chao YC, Tang HS, et al. Effects of extra-carbohydrate supplementation in the late evening on energy expenditure and substrate oxidation in patients with liver cirrhosis. JPEN J Parenter Enteral Nutr 1997;21:96-9.

98. Plank LD, Gane EJ, Peng S, et al. Nocturnal nutritional supplementation improves total body protein status of patients with liver cirrhosis: a randomized 12-month trial. Hepatology 2008;48:557-66.

99. Schrag SP, Sharma R, Jaik NP, et al. Complications related to percutaneous endoscopic gastrostomy (PEG) tubes. A comprehensive clinical review. J Gastrointestin Liver Dis 2007;16:407-18.

100. Al-Abboodi Y, Ridha A, Fasullo M, et al. Risks of PEG tube placement in patients with cirrhosis-associated ascites. Clin Exp Gastroenterol 2017;10:211-4.

101. Braegger C, Decsi T, Dias JA, et al. Practical approach to paediatric enteral nutrition: a comment by the ESPGHAN committee on nutrition. J Pediatr Gastroenterol Nutr 2010;51:110-22.

102. Wicks C, Somasundaram S, Bjarnason I, et al. Comparison of enteral feeding and total parenteral nutrition after liver transplantation. Lancet 1994;344:837-40.

103. Mohammad S, Grimberg A, Rand E, et al. Long-term linear growth and puberty in pediatric liver transplant recipients. J Pediatr 2013;163:1354-60 e1-7.

104. Perito ER, Glidden D, Roberts JP, et al. Overweight and obesity in pediatric liver transplant recipients: prevalence and predictors before and after transplant, United Network for Organ Sharing Data, 1987-2010. Pediatr Transplant 2012;16:41-9.

105. Dagher M, Ng VL, Carpenter A, et al. Overweight, central obesity, and cardiometabolic risk factors in pediatric liver transplantation. Pediatr Transplant 2015;19:175-81.

106. Sundaram SS, Alonso EM, Zeitler P, et al. Obesity after pediatric liver transplantation: prevalence and risk factors. J Pediatr Gastroenterol Nutr 2012;55:657-62.

107. Nair S, Verma S, Thuluvath PJ. Obesity and its effect on survival in patients undergoing orthotopic liver transplantation in the United States. Hepatology 2002;35:105-9.

108. Conzen KD, Vachharajani N, Collins KM, et al. Morbid obesity in liver transplant recipients adversely affects longterm graft and patient survival in a single-institution analysis. HPB (Oxford) 2015;17:251-7.

109. Valta H, Jalanko H, Holmberg C, et al. Impaired bone health in adolescents after liver transplantation. Am J Transplant 2008;8:150-7.

110. Okajima H, Shigeno C, Inomata Y, et al. Long-term effects of liver transplantation on bone mineral density in children with end-stage liver disease: a 2-year prospective study. Liver Transpl 2003;9:360-4.

111. Nightingale S, McEwan-Jackson FD, Hawker GA, et al. Corticosteroid exposure not associated with long-term bone mineral density in pediatric liver transplantation. J Pediatr Gastroenterol Nutr 2011;53:326-32.

112. Sheikh A, Cundy T, Evans HM. Growth, body composition, and bone density following pediatric liver transplantation. Pediatr Transplant 2018;22:e13201.

113. Guthery SL, Pohl JF, Bucuvalas JC, et al. Bone mineral density in long-term survivors following pediatric liver transplantation. Liver Transpl 2003;9:365-70.

114. Legarda M, Gordon G, Lloyd C, et al. Vitamin D deficiency and insufficiency after pediatric liver transplantation. Pediatr Transplant 2013;17:631-7.

Figure legends:

Figure 1: Pathophysiology of malnutrition seen in chronic and end stage liver disease

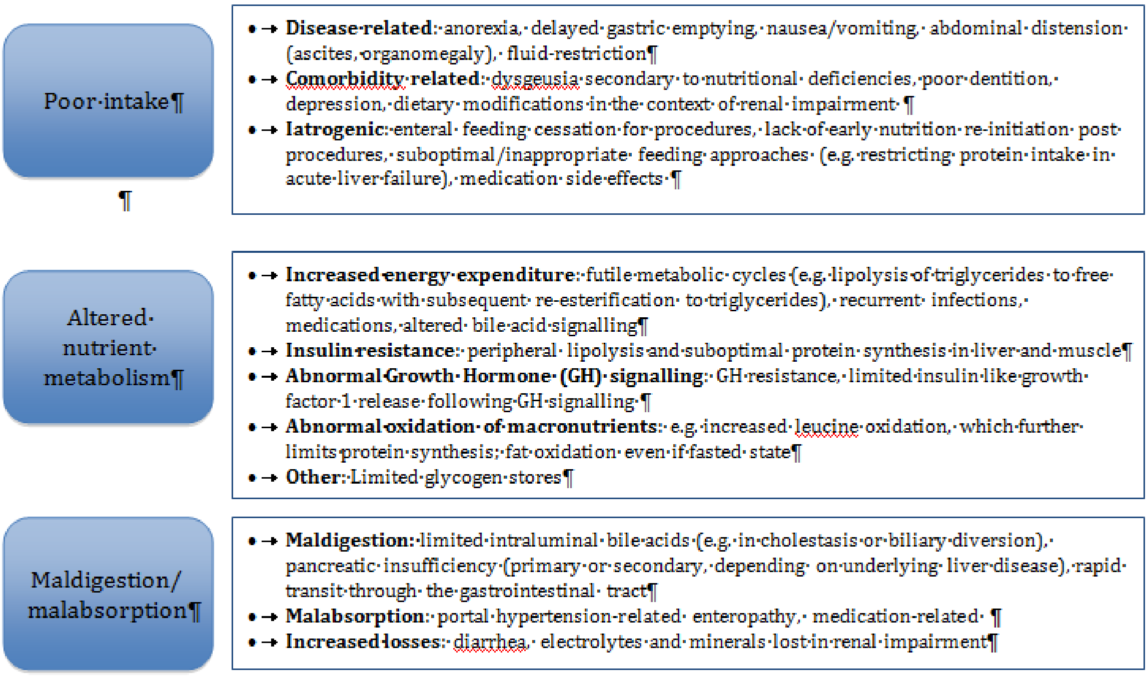

Figure 2: Approach to feeding children with end-stage liver disease

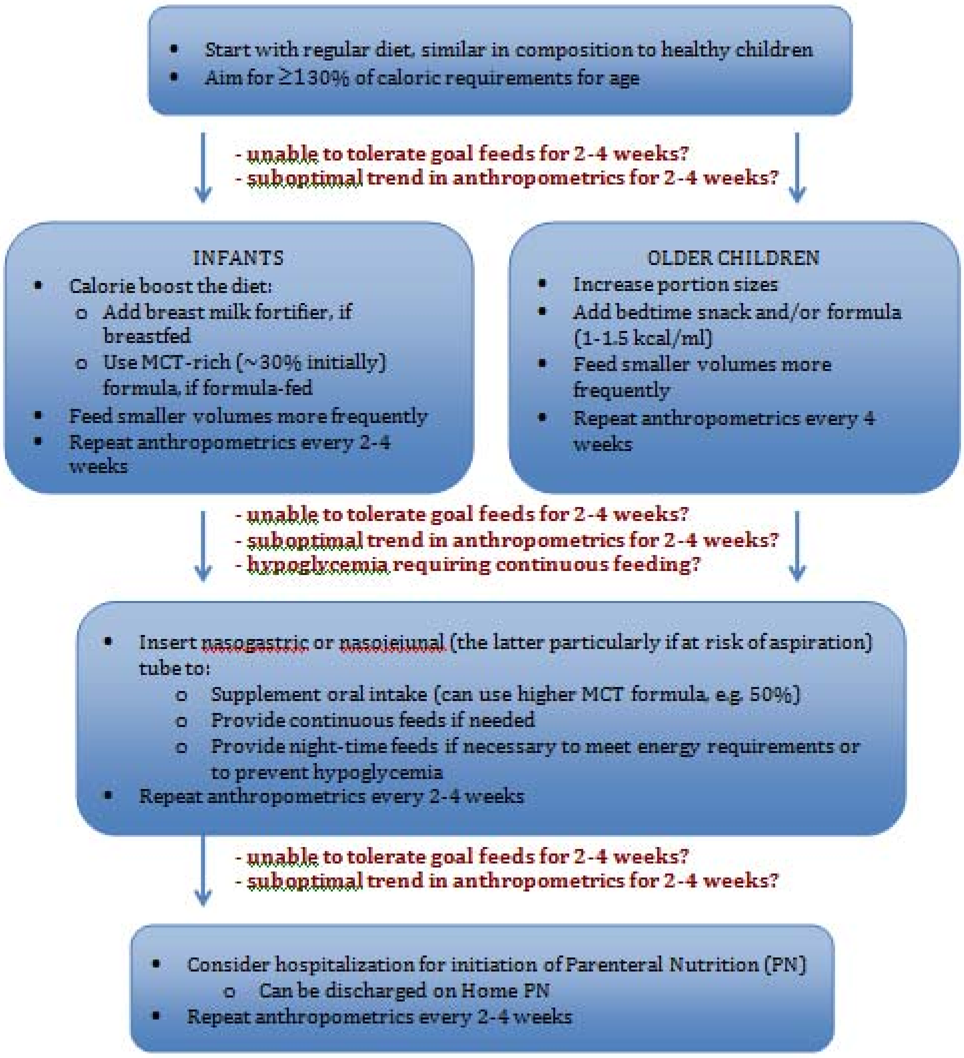

Table 1: Focused physical examination of patients with cholestatic or end-stage liver disease

	Clinical examination finding	Deficiency
General	• Edema	• Protein
HEENT	• Angular cheilitis • Glossitis • Dry eyes, decreased tears • Gingival hyperplasia	• Iron • Vitamin B complex • Vitamin A • Vitamin C
Respiratory	• Tachypnea	• Thiamine (acidosis) • Protein (excess; ammonium)
Cardio-vascular	• Tachycardia (due to heart failure) • Tachycardia (due to anemia)	• Protein, thiamine, selenium, carnitine • Iron, vitamin B12
Musculoskeletal	• Widened wrists, rachitic rosary • Fractures • Bone pain • Muscle aches or cramps	• Vitamin D • Vitamin D, vitamin K, Ca, Mg, P • Vitamin C, vitamin A (excess) • carnitine, Ca, Mg
Neurologic	• Loss of DTR, truncal and limb ataxia • Ophthalmoplegia, peripheral neuropathy • Numbness, paresthesias	• Vitamin E • Vitamin E, thiamine • EFAD
Skin	• Perifollicular keratosis • Alopecia, periorificial rashes • Dry/rough skin • Petechiae, purpura • Beau's lines in nails • Poor wound healing • Hair discoloration	• Vitamin A • Zinc • Essential fatty acid deficiency • Vitamins K/C • Protein • Protein, vitamins A/C, copper, zinc • Protein
Gastro-intestinal	• Diarrhea	• Zinc • Protein

EFAD: essential fatty acid deficiency; HEENT: Head, Ears, Eyes, Nose, Throat

Table 2: Approach to laboratory monitoring for nutritional deficiencies in patients with cholestasis or end stage-liver disease

Nutrient	How to monitor	Limitations/considerations	Re-assessment frequency
Protein	• Blood Urea Nitrogen, creatinine	• Affected by hydration status	• Every 3 months
Essential fatty acids	• Quantitative fatty acids	• Costly, not widely available	• Every 3-6 months*
Vitamin A	• Serum retinol, retinol binding protein (RBP) • Modified relative dose response	• RPB affected by hepatic synthetic function and zinc status • In cholestatic patients	• Every 3-6 months*‡
Vitamin E	• Serum vitamin E • α-tocopherol to total lipid (triglycerides, phospholipids and total cholesterol) ratio	• In non-cholestatic patients • In cholestatic patients	• Every 3-6 months*‡
Vitamin K	• INR	• Normal INR does not ensure vitamin K adequacy for bone mineralization • Affected by liver function	• Every 3-6 months*‡
Vitamin D	• 25-hydroxy-vitamin D		• Every 3-6 months*‡
Zinc	• Serum zinc • Alkaline phosphatase	• Affected by albumin levels, inflammation • Affected by bone and liver disease	• As indicated clinically, maximum every 3 months
Iron	• Ferritin • Soluble transferrin receptor	• Affected by inflammation • Affected by advanced liver disease, hemolysis, recent blood loss	• As indicated clinically, maximum every 3 months
Metabolic Bone Disease	• 25-hydroxy-vitamin D, INR • Serum calcium, magnesium, phosphate levels • Serum parathyroid hormone levels	• As above	• As indicated clinically

*depends on severity of maldigestion/malabsorption

‡fat soluble vitamin levels may need to be measured on a monthly basis in severely cholestatic infants.

INR: International Normalized Ratio

Table 3: Recommendations for nutritional support in children with cholestasis

Energy/ Nutrient	Requirement	Comments
Energy	~130% of requirement for age	• Measure REE via indirect calorimetry if available • Account for losses associated with maldigestion/malabsorption • Monitor MUAC and TSF every 2-4 weeks • Use NG/NJ feeding if unable to meet energy goals for more than 2 weeks
Fat	• 30-50% of total calories • Start with MCT/LCT=30%/70% of total fat calories • Provide a minimum of 3% of total kcal from LA and 0.7-1% from αLA	• Increase MCT if suboptimal growth with LCT (dropping weight/length-height z/scores or no evidence of catch up if already low, for 1 month) or if poor tolerance of LCT • MCT may be added in the form of both MCT oil, and MCT-containing formula. Development of steatorrhea may suggest excessive MCT supplementation • Monitor for EFAD • Dietary sources of EFA include soy, canola, corn, walnut or fish oils, as well as egg yolks.
Protein	~130-150% of requirements for age	• Account for losses associated with maldigestion/malabsorption • Provide at least minimum requirements for age
Carbohydrates	• 40-60% of total calories	• Hyperglycemia can occur due to insulin resistance • Hypoglycemia can also occur
Vitamin A‡	• <10 kg – 5,000 IU/day • >10 kg – 10,000 IU/day	• Adjust based on results of monitoring labs (see frequency of monitoring, Table 2)
Vitamin D‡	• Cholecalciferol: 2,000-5,000 IU/day	• Larger weekly doses (e.g. 50,000 IU/once per week) are used in some centers; limited available data preclude formal recommendations re: weekly dosing • Calcitriol can be used in patients with rickets/osteoporosis in the context of cholestasis/cirrhosis; limited data in pediatrics
Vitamin E‡	• TPGS: 15-25 IU/kg/day	• Adjust based on results of monitoring labs (see: Approach to laboratory monitoring for nutritional deficiencies in patients with chronic liver disease, Table 2)

Vitamin K‡	• 2-5 mg per day	• 1-10 mg IV may be required • Anaphylaxis with IV Vitamin K has been reported • May also be given IM
Iron	• Meet DRI for age	• Adjust based on results of laboratory investigations • Note that hepatotoxicity from iron overload can occur; clinicians should carefully consider the need for IV iron provision
Calcium	• Meet DRI for age	• Adjust based on results of laboratory investigations • Increase calcium and decrease oxalate intake in cholestatic patients with oxalate stones
Sodium	• 1-2 mEq/kg/day	• Restrict if fluid overloaded
Potassium	• 2 mEq/kg/day	• Adjust based on results of laboratory investigations

αLA: α-Linolenic Acid; DRI: Dietary Reference Intake; EFA: Essential Fatty Acids; EFAD: Essential Fatty Acid Deficiency; IM: Intramuscular; IU: International Units; IV: Intravenous; kcal: kilocalories; LA: Linoleic Acid; LCT: Long Chain Triglycerides; MCT: Medium Chain Triglycerides; MUAC: Mid Upper Arm Circumference; NG: Nasogastric; NJ: Nasojejunal; REE: Resting Energy Expenditure; TPGS: D-a-tocopheryl Polyethylene Glycol 1000 Succinate; TSF: Triceps Skin Folds

‡Supplementation with all fat-soluble vitamins together may improve their absorption

Table 4: Summary of Recommendations made in this Position Paper

Chronic Cholestatic Liver Disease	
1.	Beyond weight and height measurements, clinicians should monitor MUAC and TSF serially in patients with chronic liver disease. The frequency of the measurements depends on the nutritional status and can range from every two weeks to 3 months.
2.	A careful, nutrition focused, physical examination is recommended in every clinic visit.
3.	Clinicians should familiarize themselves with the limitations of nutritional biomarkers in the context of chronic liver disease
4.	Nutrition support of cholestatic infants should be optimized to prevent and treat nutritional deficiencies. A detailed approach to optimizing nutrition support is provided in Table 3.
Cirrhosis/End-stage Liver Disease	
5.	Nutritional status, growth and eating habits should be closely monitored. The frequency of monitoring depends on the severity of malnutrition and severity of liver disease and can range from every 2 weeks to every 3 months.
6.	Increased feeding frequency, increased caloric density of consumed foods and use of modular supplements should be used as needed.
7.	Nasogastric/nasojejunal feeding should be considered, when appropriate.
8.	Parenteral nutrition can be used when enteral nutrition (oral, gastric and jejunal) is not tolerated or fails to achieve growth targets.
Post Liver Transplantation (LTx)	
9.	A formal assessment of nutritional status is recommended for all children before and after liver transplantation, the frequency of which depends on the nutritional status and can range from every 2 weeks to every 3 months and should occur until adequate growth patterns (achieve at minimum BMI>-1 SD and/or MUAC>-1 SD without deceleration in weight for length z-score) are established post-LTx.
10.	Nutritional interventions (provision of appropriate calories to achieve MUAC and TSF>10th percentile for age, correction of micronutrient deficiencies) to optimize nutritional status in the peri-transplant period should be implemented, as they are associated with improved patient outcomes.
11.	Liver transplant recipients should be screened for overweight/obesity and hypertension at every routine medical encounter. Patients should also be tested for other metabolic syndrome-related complications, such as dyslipidemia and insulin resistance at minimum annually.
12.	Monitoring of bone health is advised in liver transplant recipients; particularly the first 2 years post LTx. Monitoring with laboratory investigations should occur every 3-6 months.

BMI: Body Mass Index; DXA: Dual energy X-ray Absorptiometry; LTx: Liver Transplantation; MUAC: Mid Upper Arm Circumference; SD: Standard Deviation; TSF: Triceps Skin Folds