Nutritional Considerations in Pediatric Liver Disease

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Within the last 60 years, pediatric hepatology has seen many advances in improvement in timely diagnosis and management of chronic liver disease and also in liver transplantation. Growth failure and malnutrition have always been important factors in the treatment of children with liver disease, specifically cholestatic liver diseases. The liver has a central function in nutrient metabolism, and the abnormalities seen in chronic liver disease result in nutritional and metabolic deficiencies. Nutritional needs are dependent on the type of liver disease, age of the patient, and whether the disease is acute or chronic. In the setting of acute liver disease, such as acute viral hepatitis, malnutrition is unusual; however, in fulminant liver failure, nutritional modifications are needed to manage hepatic encephalopathy. Chronic liver disease may be cholestatic or noncholestatic and in most instances is associated with malnutrition.

Cholestatic injury to the liver reflects a diverse group of diseases, resulting from biliary obstruction, disorders of bile synthesis or transport, metabolic and endocrine disorders, infections, and toxic effects. The most common is biliary atresia, occurring in approximately 1 of 10,000 live births; it is the most common indication for liver transplantation in children. Patients have relatively progressive hepatic disease and, often, poor nutritional status, making preoperative management of malnutrition a challenge.

Malnutrition is a negative prognostic indicator of overall survival, and the inability to improve nutritional status before surgery increases the risk of postoperative complications and mortality. Adequate nutrition allows for growth, improved immunologic status, and improved transplantation outcomes.

Nutritional status in the setting of liver disease can be difficult to assess. Weight alone is not a sufficient marker for nutritional status, especially if the patient has ascites or organomegaly: fluid retention and a disproportionately large organ may result in substantial weight gain, whereas the overall nutritional status is actually poor. The ascites and organomegaly, as well as portal hypertension, can also contribute to poor oral tolerance, furthering the failure to gain appropriate weight for age and preventing the often needed catch-up weight gain. Although serial abdominal circumference measurement may aid in determining whether weight gain is secondary to ascites, it is an imprecise way of differentiating true weight gain from fluid gain. More accurate measures include triceps skinfolds and middle upper arm circumference measurements, with standards for age available from the World Health Organization. These measurements, however, require calipers and training in proper technique. Peripheral edema is a potential cause of overestimation of both measures and if present needs to be considered.

Both the child's age and the specific disease affecting the liver contribute to the issues of nutrition and growth facing each patient. Assessment and support are key components of effective care, which is best performed by a team of physicians

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and nutritionists with knowledge and expertise in treating children with chronic liver disease.

The characteristic physical findings in infants and children with cholestatic liver disease suggest why weight for age alone is not sufficient in the assessment of nutritional status. Body habitus typically is marked by thin limbs and a protuberant abdomen. A decrease in middle upper arm circumference is often the earliest change in progressive disease, with triceps skinfold thickness the next measure to decrease. As abdominal girth increases, it may equal and eventually exceed thoracic girth. Unless rickets develops early in the disease from vitamin D deficiency, height for age is the last anthropometric measure to decrease. Even with adequate nutritional support, further delay in linear growth can continue despite improvement in body weight.

The factors that affect nutrition are 4-fold:

- hypermetabolism and increased energy needs,
- malabsorption and poor use of calories,
- anorexia, and
- disordered use of nutrients absorbed.

Growth impairment in cholestatic liver disease is related to the lack of intraluminal bile acid, leading to fat malabsorption. Hepatocellular dysfunction and portal hypertension also play a role, but fat malabsorption is primary. Also contributing to poor linear growth is the decreased liver production of insulin-like growth factor seen with hepatocyte loss.

To counteract malabsorption, poor use of nutrients, and a resting energy expenditure 30% to 40% greater than normal, total caloric intake must be increased. The estimated energy requirement in affected infants may be as much as 150% of what healthy infants need, and for older children, the figure ranges from 120% to 170%. Beyond total energy, nutritional requirements are broken down into carbohydrate, specific fat, and protein requirements, as well as specific vitamin and micronutrient needs. Carbohydrates provide most calories and are important in helping to maintain normoglycemia: children with chronic liver disease are prone to hypoglycemia during fasting states because of reduced gluconeogenesis and glycogen storage capacity. Glucose is preferred to galactose and other sugars to avoid potential intolerances. Short-chain polymers are preferred to both high monomer-containing diets with increased osmotic loads and to starches, which may be malabsorbed and lead to colonic fermentation, bloating, and diarrhea.

Fat is calorically dense and also provides essential polyunsaturated fatty acids. With the fat malabsorption and steatorrhea that are characteristic of cholestatic liver diseases, although increasing total fat intake increases overall fat absorption, it will also lead to increases in diarrhea and steatorrhea. Medium chain triglycerides (MCTs) are a readily available source of energy and are absorbed directly from the venous blood without the need for bile and emulsification. Supplying 30% to 70% of total fat as MCTs provides adequate fat calories, reduces malabsorption of fat and steatorrhea, and improves weight gain. However, providing all fat calories as MCTs can lead to essential fatty acid (EFA) deficiency. The EFAs are linoleic acid and α-linolenic acid, which are not produced by the body but are necessary for production of long-chain polyunsaturated fatty acids and are important in brain and eye development. To prevent deficiency, approximately 10% of energy should be provided as supplemental EFAs, with a ratio of linoleic to α-linolenic acid of 1:5 to 1:15. Certain dietary oils (walnut, canola, sunflower, and soybean), as well as fish oils and egg yolks, can be used in oral and enteral tube feeding to provide additional fat calories. Formulas with adequate amounts of MCTs as a proportion of total fat calories are recommended for infants with cholestatic liver disease. Older children may benefit from MCT oil supplementation to their meals.

Amino acid metabolism is altered in chronic liver disease, with branched-chain amino acid levels decreased and aromatic amino acid levels increased. Branched-chain amino acid supplementation may reduce protein catabolism, improve nitrogen retention, and improve protein synthesis. Children with chronic liver disease typically require 2 to 3 g/kg daily as the protein intake sufficient for growth. With hepatocyte loss, liver insufficiency, and portosystemic shunting, protein intake can lead to hyperammonia. Nonetheless, protein restriction should not be used to reduce ammonia levels; rather, hyperammonemia should be treated with lactulose or sodium benzoate.

Fat malabsorption can lead to deficiency of the fat soluble vitamins (A, D, E, and K). Other vitamins and minerals can be deficient as well, and proper monitoring is important. Supplementation, available in an oral water soluble form, with vitamins A, D, E, and K is recommended for all children with cholestatic liver disease (Table). Water soluble vitamins should be supplemented at twice the recommended daily allowance because of the risk of altered metabolism by the diseased liver. Trace elements (calcium, zinc, magnesium, and selenium) should be supplemented based on the patient's plasma levels. Careful attention should be paid to the potential for copper toxicity in the setting of cholestasis, and serum levels should be drawn during nutritional assessments. Iron

supplementation is not routinely recommended because iron deficiency is not common in the absence of chronic blood loss.

Total daily fluid requirements are the same as for a healthy child unless there is a concern about fluid retention and ascites. Although careful attention should be paid to electrolytes, correction of hyponatremia should generally be avoided because raising the sodium level can exacerbate fluid retention.

Oral feeding should be encouraged as long as nutritional needs can be met as evidenced by adequate growth and development. Oral tolerance is often affected in chronic liver disease by ascites, organomegaly, gastroesophageal reflux, and dyspepsia, which can lead to anorexia, early satiety, nausea, and vomiting. With cholestatic disease, MCT-containing formula should be the milk for bottle-fed infants and should be used to supplement breastfed infants. Fortification of the formula is another option to increase energy intake. Developmentally appropriate foods (first purees and later solids) should be encouraged to promote oral feeding and prevent oral feeding aversion.

When energy needs cannot be met orally, enteral feeding via nasogastric tubes is an effective alternative. Nasogastric

TABLE. **Fat Vitamin Deficiencies**

VITAMIN	SOURCE	DEFICIENCY	TOXIC EFFECTS	MEASUREMENT	SUPPLEMENTATION
Vitamin A	Retinyl palmitate (animal sources)—fish oils, liver, dairy Carotenoids (plant sources)—green vegetables, orange-colored fruit, and vegetables)	Night blindness, xerophthalmia Dry skin Possible immune dysfunction	Liver fibrosis, hypercalcemia, pseudotumor cerebri, painful bone lesions	Serum retinol, serum retinol/RBP ratio, retinal dose response test, liver retinol level	5000-25,000 U/d, coadministered with TPGS for improved absorption
Vitamin D	Synthesized in skin with exposure to UV-B light Food sources: fortified dairy products and fish oil	Hypocalcemia, hypophosphatemia, muscle hypotonia, and rickets	Hypercalcemia and pseudotumor cerebri	25-Hydroxyvitamin D serum levels (measure serum ionized calcium and phosphorus)	400 IU/d, 25-hydroxyvitamin D_3 preferred Supplementation should be given with adequate calcium and phosphorus 25-Hydroxyvitamin D serum levels >20 ng/mL
Vitamin E	α-Tocopherol highest bioavailability Nuts, green leafy vegetables, and vegetable oil	Poor nerve conduction, leading to hypo- or areflexia, ataxia, peripheral neuropathy, and myopathy Vision loss Hemolytic anemia	Impaired neutrophil chemotaxis	Vitamin E (serum tocopherol)/total lipid ratio (>0.8 mg/g normal)	Oral TPGS-E supplementation 15-25 IU/kg daily preferably as TPGS
Vitamin K	Dietary source: vitamin K_1 (phylloquinone)—green leafy vegetables, dairy products, and liver Enteric bacteria derived: vitamin K_2 (menaquinones)	Hemorrhagic disease Synthesis of uncarboxylated proteins (coagulation factors: II, VII, IX, X, and protein C and S)		Prothrombin time or INR PIVKA II assay (proteins induced in vitamin K absence)	Orally 2.5-5 mg/d Intravenous, intramuscular, or subcutaneous administration may be necessary

Abbreviations: INR=international normalized ratio; PIVKA=Proteins Induced by Vitamin K Absence; RBP=retinal-binding protein; TPGS=D-α-tocopheryl polyethylene glycol succinate; TPGS-E=vitamin E D-α-tocopheryl polyethylene glycol succinate.

feeding can be performed at home overnight as supplementation to daytime oral feeds, which should be encouraged to maintain feeding skills. Gastrostomy feeding is not a route of choice because placement of the gastrostomy tube can be complicated by organomegaly, ascites, and bleeding risks.

Used only when enteral feeding cannot meet a child's nutritional needs, parenteral nutrition is a last resort that comes with its own sets of concerns: the risk of sepsis from central catheter infections and additional parenteral nutrition–related toxic effects to the liver.

Malnutrition and growth failure in children with liver disease are multifactorial. Despite advances in management, malnutrition has remained a challenge, and nutritional support is a central goal in the care of these children. Malnutrition has been associated with poor outcomes. Assessment of nutritional status is complicated by changes in body habitus and fluid retention. Children with chronic cholestatic liver disease have increased overall caloric needs, as well as specific needs in the composition of their intake of macromolecules. Attention must also be paid to micronutrient and vitamin deficiencies. Care is best provided within a multidisciplinary team, including primary care physicians, hepatologists, transplant surgeons, nutritionists, or dieticians with expertise in liver disease, social workers, and feeding therapists.

COMMENTS: Pediatric hepatology has indeed seen great advances during the past several decades. One of the first patients I had the privilege of caring for at the start of my career in the 1980s was a girl born with biliary atresia. For the first 6 years of her life, this girl invested nearly all her energy in scratching, never able to relieve the intense itching from her jaundice. She barely spoke and did not play. She scratched. She scratched until the xanthomas that covered her body bled. So small for her age, she actually looked younger than her sister, who was born a year or two after her. However, when she was 6, this girl had her life transformed. She went to Pittsburgh to receive one of the earliest pediatric liver transplantations. She did not need to scratch any more.

– Henry M. Adam, MD
Editor, *In Brief*

CME Quiz Correction

In the December 2013 article "Managing Feeding Problems and Feeding Disorders" (Phalen JA. *Pediatrics in Review.* 2013;34:549, doi: 10.1542/pir.34-12-549), the correct answer to Question 4 should be: "A. Drools constantly and dribbles food from mouth." In the online version of the journal, a correction has been posted with the article, and the online quiz has been updated to reflect the correct answer. The journal regrets the error.

ANSWER KEY FOR NOVEMBER 2014 PEDIATRICS IN REVIEW:
Pediatric Hearing Loss: 1. D; 2. B; 3. A; 4. C; 5. C.
Spirometry for the Primary Care Pediatrician: 1. E; 2. A; 3. E; 4. A; 5. D.
Respiratory Failure: 1. B; 2. D; 3. E; 4. B; 5. E.

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