8A. Nutritional Requirements of Preterm and Term Infants, Children, and Adolescents

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Children have different nutritional requirements at different ages. Caloric requirements are highest in infancy and decrease with age (Table 1).

Table 1. Caloric Requirements/kg Body Weight

<table>
<thead>
<tr>
<th>Age</th>
<th>kcal</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0–6 months</td>
<td>108</td>
<td></td>
</tr>
<tr>
<td>6–11 months</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>1–3 years</td>
<td>102</td>
<td></td>
</tr>
<tr>
<td>4–6 years</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>7–10 years</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Males 11–14 years</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Males 15–18 years</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Females 11–14 years</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Females 15–18 years</td>
<td>40</td>
<td></td>
</tr>
</tbody>
</table>


I. Preterm infant: goal weight gain is 15–20 g/kg/day
   A. Optimal nutrition is critical
   B. Preterm infants should be given early aggressive enteral/parenteral nutrition (Table 2)

Table 2. Enteral and Parenteral Intake

<table>
<thead>
<tr>
<th>ENTERAL INTAKE</th>
<th>PARENTERAL INTAKE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELBW (&lt;1,000 g)</td>
<td>VLBW –LBW (1,000-1,500 g)</td>
</tr>
<tr>
<td>Energy per kg/day</td>
<td>130–150 kcal</td>
</tr>
<tr>
<td>Protein per kg/day</td>
<td>3.8–4.4 g</td>
</tr>
<tr>
<td>Carbs per kg/day</td>
<td>9–20 g</td>
</tr>
<tr>
<td>Fat per kg/day</td>
<td>6.2–8.4 g</td>
</tr>
<tr>
<td>Vit A per kg/day</td>
<td>700–1500 IU</td>
</tr>
<tr>
<td>Vit D per kg/day</td>
<td>150–400 IU</td>
</tr>
<tr>
<td>Ca per kg/day</td>
<td>100–220 mg</td>
</tr>
<tr>
<td>P per kg/day</td>
<td>60–140 mg</td>
</tr>
</tbody>
</table>

C. Enteral Nutrition
1. Preterm infant formula and preterm human milk fortifiers for breastmilk are required for appropriate weight gain and bone mineralization
2. Preterm formulas meet the special requirements of preterm infants for:
   a. Protein content
      1) Higher content results in increased protein accretion and weight gain
      2) Whey predominant, cow milk–based
   b. Fat
      1) Fat blends consist of 40%–50% MCT (MCT delivers adequate fat calories despite low intestinal lipase or bile salt concentration)
      2) Preterm formula fat blends also contain essential fatty acids
   c. Carbohydrate
      1) Contain carbohydrate blends of lactose and glucose polymers
      2) 40%–50% of calories come from carbohydrates
   d. Minerals
      1) Calcium and phosphorus: preterm formulas contain 165–180 mg of Ca/100 kcal and 82–100 mg of P/100 kcal (term infant formulas contain 53–76 mg of Ca/100 kcal and 42–57 mg of P/100 kcal)
      2) Magnesium content higher than in term formulas
      3) Iron: provides 2–4 mg/kg until 12 months of age
   e. Vitamins
      1) Vitamin content is higher than standard formula and is such that no additional MVI supplementation is necessary
D. Parenteral nutrition as a supplement to gradual introduction of full enteral feeding
1. Protein
   a. Should be provided within 24 hours of birth at a minimum of 1.5–2 g/kg per day due to rapid loss of protein stores with glucose infusion alone
2. Carbohydrate
   a. Glucose infusion rates should start at 6 mg/kg/min and slowly increased to 11–12 mg/kg/min
3. Fat
   a. 20% intralipid preparation is superior to the 10% solution because of the lower phospholipid emulsifier content
   b. Administer lipid emulsion continuously over 24 hours at initial dose of 1–2 g/kg, increasing 3 g/kg maximum
   c. Requires close monitoring of serum triglyceride to keep serum levels <200 mg/dL
4. Trace Minerals
   a. Additional selenium, zinc, manganese, copper and cobalamin are essential
   b. Copper and manganese should be cautiously administered in the presence of obstructive jaundice
II. Term Infant
A. Caloric requirement:
   1. 95–115 kcal/kg/day for the first 6 months of life
   2. 40%–60% from carbohydrate
   3. 30%–50% from fat
   4. 8%–12% from protein
B. Ideal weight gain:
   1. 25–30 g/d for the first 3 months
   2. 15–20 g/d for the second 3 months
   3. 10–15 g/d for the next 6 months
C. Infant formulas in the US are standardized to contain adequate minerals and vitamins to meet the needs of healthy infants in the first year of life
   1. Calcium: 210 mg/day for first 6 months. 270 mg/day 7–12 months
   2. Vitamin D: RDA for infants is 400 IU/day
   3. Iron: RDA for infants 0–6 months 0.27 mg/day, for infants 7–12 months is 11 mg/day
   4. Zinc: RDA for infants 2 mg/day
   5. Fluoride: 0.25 mg daily supplementation recommended in infants over 6 months of age consuming nonfluoridated water
III. Prepubertal Children
   A. Caloric requirement 70–90 kcal/kg/day
   B. Protein: normally 1–1.2 g/kg/day
   C. Fat: 30%–40% of total calories for children 1–3 years. From age 3 to adulthood, no more than 25%–35% of total daily calories

IV. Adolescent (Pubertal)
   A. Increased energy requirements:
      1. Estimated energy requirement for girls and boys ages 11–14 years is 45 and 55 kcal/kg/day, respectively
      2. Requirement decreases to 40–45 kcal/kg/day between 15–18 years
   B. Protein requirement estimated at 0.85 g/kg/day
   C. At risk for inadequate Ca and vitamin D intake
      1. Recommended intake of Ca for both males and females (ages 9–18 years) is 1,300 mg/day
   D. Females are at increased risk of iron deficiency due to menstrual losses

Recommended Reading


8B. Comparison of Human Milk and Cow Milk–based Formula

Lay Har Cheng, MD, MSPH
Conrad Cole, MD, MPH, MSc

I. Human Milk—Nutrition and Production
Nutritional content of human milk is variable, between women as well as between feeds in the same individual. All outlines of nutritional content of human milk are averages

A. Stages of human milk production
1. Colostrum is the fluid secreted by the mammary glands in the first few days after birth
   a. Higher in protein than transitional or mature milk
2. Transitional milk is produced starting 2–5 days postpartum for 10–14 days
   b. Higher in fat than colostrum or mature milk
3. Mature milk is produced starting 10–14 days postpartum
   a. Higher concentration of lactose than colostrum or transitional milk
   b. Foremilk is the milk first sucked by the baby and is thinner and lower in fat, providing hydration. This is followed by hindmilk, which is richer in fat content and high in calories

II. Proteins
A. Mature human milk
   1. Produced after term infant delivery
      a. Contains 70% whey and 30% casein
      b. Peak total protein content of term birth colostrum is approximately 2.3 g/dL
      c. Protein content of mature milk is approximately 1g/dL
   2. Produced after preterm infant delivery
      a. Contains 70% whey and 30% casein
      b. The more immature the infant at birth, the higher the protein level in maternal milk at same number of weeks postpartum for at least the first 8 weeks
         1) Protein content of preterm human milk is still considered inadequate for growth in the preterm infant
   3. Whey protein in human milk consists of ~99% α-lactalbumin, but also includes lactoferrin, lysozyme and secretory IgA. The latter three are resistant to intraluminal digestion and thus aid in infant immune defenses

B. Standard cow milk protein-based formula (20 kcal/oz)
   1. Whey-to-casein ratio ranges from 18:82 (resembling ratio in whole cow milk) to 100:0
   2. Total protein concentration is approximately 1.4–1.7 g/dL
   3. Whey protein in cow’s milk is ~65% β-lactoglobulin, ~25% α-lactalbumin and ~8% albumin. β-lactoglobulin is the major antigen responsible for cow milk protein allergy

III. Lipids
A. Mature human milk
   1. Produced after term infant delivery
      a. Lipid content variable between individuals, diurnally and day-to-day, but is ~3.5 g/dL
      b. Lipid content increases throughout a feed from foremilk to hindmilk, and also increases over the total duration of lactation in months
      c. Lipids account for ~50% of the calorie content of human milk
      d. Lipid content of breast milk is unrelated to maternal diet
2. Produced after preterm infant delivery
   a. Higher fat content than milk produced after full-term delivery
   b. Lipid composition – 98% triglyceride, 0.8% phospholipid and 0.5% cholesterol
      1) Majority of triglyceride is long-chain fatty acids—palmitic, oleic, linoleic and linolenic
      2) Arachidonic acid (ARA) and docosahexaenoic acid (DHA) are also long-chain fatty acids in milk
      3) Medium-chain fatty acids make up <12% of the total fatty acids

B. Standard intact cow milk protein-based formula
   1. Total fat content is similar or greater than human milk, ranging 3.4–3.8 g/dL
   2. Lipids account for 40%–50% of calories in formula
   3. Increased proportion of passively absorbed medium-chain fatty acids and decreased long-chain fatty acids than human milk to better match the absorption of human milk
   4. Composition of fats varies by brand, but generally consists of various vegetable oils
   5. ARA and DHA added to most formulas

IV. Carbohydrate
   A. Mature human milk
      1. Main carbohydrate is lactose, approximately 7 g/dL
      2. Contributes 40% of total calories
   B. Standard intact cow milk, protein-based formula (Table 1)
      1. Usual carbohydrate is lactose, but some brands use combinations of glucose, corn syrup solids, rice starch and maltodextrin, with or without lactose
      2. Carbohydrate content is fairly standard at 7 g/dL
      3. Contributes 40% of total calories

V. Minerals

Table 1. Estimated Micronutrient Content of Preterm, Term and Standard Cow Milk Formula

<table>
<thead>
<tr>
<th>Mineral (per L)</th>
<th>Mature preterm milk</th>
<th>Mature term milk</th>
<th>Standard cow milk formula (20 kcal/oz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron (mg)</td>
<td>0.9</td>
<td>0.3–0.9</td>
<td>10–12.2</td>
</tr>
<tr>
<td>Calcium (mg)</td>
<td>220</td>
<td>200–250</td>
<td>420–570</td>
</tr>
<tr>
<td>Magnesium (mg)</td>
<td>40</td>
<td>30–35</td>
<td>41–54</td>
</tr>
<tr>
<td>Phosphorous (mg)</td>
<td>125</td>
<td>120–140</td>
<td>255–380</td>
</tr>
<tr>
<td>Zinc (mg)</td>
<td>2.8</td>
<td>1–3</td>
<td>5–6.8</td>
</tr>
<tr>
<td>Copper (mg)</td>
<td>0.63</td>
<td>0.2–0.4</td>
<td>0.47–0.61</td>
</tr>
</tbody>
</table>


A. Mature Human Milk
   1. Although the concentrations of most minerals in human milk are lower than those in cow milk, mineral bioavailability is higher from human milk
   2. Iron: Iron in breastmilk is highly bioavailable; however, exclusively breastfed infants absorb only ~0.15 mg of iron daily, relying on their own iron stores to meet the daily need of 0.75 mg. Iron stores are typically exhausted by 5–6 months postpartum in term infants. Infants require complementary foods to provide the additional 0.6 mg absorbed iron after 6 months
   3. Calcium and magnesium content constant in mature milk and adequate to meet term infant needs
4. Phosphorous declines during lactation but is still adequate to meet nutritional needs of term infants
5. Zinc and copper content of breast milk are highest in colostrum, but quickly decline to stable levels in mature milk that are adequate for nutritional needs until about 6 months postpartum

B. Preterm Milk
1. Preterm milk is inadequate to meet iron, calcium, phosphorous and zinc needs of premature infant, and must be fortified or the infant must receive supplements

C. Standard intact cowmilk, protein-based formula
1. If manufactured in the U.S. must meet guidelines for nutrient content set in The U.S. Infant Formula Act of 1980

VI. Vitamins
A. Human milk
1. Vitamin D
   a. Per Institute of Medicine (IOM), recommended dietary allowance (RDA) is 10 µg/day or 400 IU/day
   b. Mature milk contains ~ 0.33 µg/L vitamin D (13.2 IU/L) which is inadequate for nutritional needs. Supplementation required
2. Vitamin K
   a. Per IOM, adequate intake is 2.0–2.5µg/day.
   b. Mature milk contains ~ 2–3µg/L. Infants do not achieve adequate serum levels until ~6 weeks after birth if exclusively breastfed
   c. Subcutaneous or intramuscular injection of 0.5–1.0 mg phytonadione (Vitamin K1) at birth prevents Vitamin K deficient bleeding in healthy newborns

B. Cow milk formula
1. Vitamin D and K are adequate to meet nutritional needs by law. However, minimum volume required to meet RDA varies by formula from 800 mL to 1 liter/day

VII. Substances found only in human milk
A. Digestive enzymes
1. Amylase aids in digestion of starches. Infant pancreas does not secrete amylase until approximately 6 months of age
2. Bile-salt stimulated lipase aids in digestion and absorption of lipids in infants fed human milk. Heating or pasteurization of expressed breast milk destroys lipase and decreases absorption of lipids

B. Host defenses
1. Secretory IgA provides passive immunity to antigens to which mother is exposed
2. Human milk has small amounts of IgM, IgD, IgG and IgE
3. Lactoferrin in human milk has bacteriostatic and bacteriocidal effects
4. Human milk lysozyme – bacteriocidal and antiinflammatory
5. Human milk macrophages aid in protection against gut pathogens

C. Growth factors – higher concentrations in colostrum than in mature milk
1. Epidermal growth factor – cytokine stimulates growth of intestinal mucosa and epithelium, strengthening barrier function
2. Human milk growth factor promotes growth of intestinal mucosa
3. Insulin-like growth factor promotes growth of intestinal tract

D. Hormones
1. Thyroxine and thyrotropin-releasing hormone – may mask congenital hypothyroidism in the first few months of life
2. Cortisol – correlates with maternal serum cortisol levels
3. Cholecystokinin – enhances digestion, sedation and satiety
4. Prostaglandins – cytoprotection of gastrointestinal epithelium
Recommended Reading


I. The use of special infant formulas should be justified by a specific diagnosis
   A. Prematurity
   B. Lactose intolerance
   C. Protein allergy
   D. Congenital metabolic disorders
   E. Short bowel syndrome
   F. Inflammatory disease associated with malabsorption
   G. Pancreatic insufficiency
   H. Hepatobiliary disorders

II. Special formulas
   A. Formula for premature infants
      1. Usually contains more protein than standard cow milk-based formulas
      2. Caloric concentration is often increased
      3. Fat content is enriched with medium-chain triglycerides to improve fat and calcium absorption (usually 40%–50% MCT)
      4. Carbohydrates usually in the form of lactose, maltodextrin and glucose polymers
         a. Preterm infants have lower intestinal lactase activity than term infants
         b. Carbohydrate polymers allow osmolality to remain <300 mOsm/kg of water
      5. Contain more calcium than standard cow milk-based formulas (up to 2.5x) with calcium:phosphorus ratio usually ~2:1
      6. 2–2.5 times more vitamin A and D
   B. Soy-based formula
      1. Soy protein isolate must be supplemented with L-methionine and taurine
      2. Carbohydrates are sucrose, corn syrup solids and/or maltodextrin
      3. Nonmedical indications include vegetarian parents and parents with religious beliefs that forbid use of animal-based formulas
      4. Infants with galactosemia can safely drink soy-based formula
      5. 30%–64% of patients with cow milk protein-induced enteropathy are sensitive to soy protein and may require hydrolyzed protein or amino acid–based formulas
      6. Soy-based formulas are not recommended for premature infants, infants <1,800 grams, patients with renal disease (soy-based formulas contain aluminum) and infants with fructose intolerance
   C. Protein hydrolysate formula (semielemental)
      1. Protein hydrolysate formulas contain casein and/or whey which have been heat-treated and enzymatically hydrolyzed into short peptide chains and free amino acids
      2. Protein hydrolysate formulas are recommended for infants who are intolerant to intact cow milk and soy proteins
         a. Partially hydrolyzed formulas (i.e., Alfare®, Althera®, Good Start®) usually contain bigger peptides (1,500 kDa), and can induce allergic reactions
         b. Extensively hydrolyzed formulas (i.e., Pregestimil®, Nutramigen®, Alimentum®, Nutren junior®, Peptamen junior®) usually contain only free amino acids and peptides <1,500 kDa (at least 96% of peptides are <1,000 kDa, and no more than 4% of peptides between 1,000 and 2,000 kDa)
         c. Extensively hydrolyzed formulas are still immunogenic, but do not provoke reactions in 90% of infants or children with confirmed cow’s milk allergy
3. Uses:
   a. Short bowel syndrome
   b. Food protein allergy
   c. Autoimmune enteropathy
   d. HIV-associated enteropathy
   e. Pancreatic insufficiency and hepatobiliary disorders
4. Formulas derived from whey require supplemental L-cysteine, L-tyrosine and L-tryptophan to increase their biological value
5. The carbohydrates are sucrose or glucose polymers (lactose free)
6. Contain medium-chain triglycerides as they bypass the lymphatic system, and require less pancreatic lipase and bile salts for absorption (usually no more than 55% MCT, as it increases the formula osmolality)
7. Indications for high content of medium-chain triglycerides include: liver disease, cystic fibrosis, lymphangiectasia and chylothorax
D. Free amino acid formula (elemental)
   1. The protein precursors in these formulas (i.e., Neocate®, Vivonex pediatric®, Elecare®) are 100% free amino acids and are designed for infants with food allergy and short bowel syndrome
   2. These formulas are considered hypoallergenic
   3. Have a higher osmolarity than hydrolyzed formulas
   4. Lipids are a mixture of safflower, sunflower, coconut (medium-chain triglycerides) or soy oil
   5. Carbohydrates in these formulas are corn syrup and/or maltodextrin
   6. Some brands that contain soy oil may be contaminated with soy protein

Recommended Reading


I. Assessment Requirements
The assessment of an infant or child for malnutrition requires objective measures, including anthropometrics measurements, BMI and biochemical measures of malnutrition. The assessment should also incorporate calculation of energy expenditures to understand the degree to which the child is not meeting their nutritional goals.

II. Anthropometric Measurements
A. Weight, length, head circumference
   1. Infant weight: nude weight to the nearest gram
   2. Length <2 years of age requires length board with movable footboard
   3. Length >2 years of age requires stadiometer for erect height
   4. Head circumference is measured from birth to 3 years of age
B. Underweight children
   1. Stunting: body weight proportional to length, but small for age. May be the result of chronic under-nutrition
   2. Wasting: low body weight in reference to length. May be the result of acute or subacute nutritional deprivation

III. Waterlow Criteria for Malnutrition (Table 1)
A. Acute malnutrition
   1. Described as the percent of the ideal body weight for the patient's height
   2. Divide current weight by 50th percentile weight for patient's height x 100
B. Chronic malnutrition
   1. Described by the index of linear growth
   2. Divide current height by ideal height for age x 100

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height for age (%)</td>
<td>95</td>
<td>90-95</td>
<td>85-90</td>
<td>85</td>
</tr>
<tr>
<td>Weight for age (%)</td>
<td>90</td>
<td>80-90</td>
<td>70-80</td>
<td>70</td>
</tr>
</tbody>
</table>

Decreased height for age suggests chronic malnutrition (stunting);
Decreased weight for age suggests acute malnutrition (wasting).
Adapted from Waterlow (1973).

C. Z score
   1. Number of standard deviations (SD) that a height or weight value differs from the mean height and weight for child's age

D. BMI—Body mass index (kg/m2)
   1. Best anthropometric indicator of adiposity
   2. Overweight: BMI 85-95 percentile for age
   3. Obese: BMI >95 percentile for age
IV. Body Composition Methodologies
A. Skinfold thickness: direct measurement of fat. Method not fully validated in children
B. Mid-Arm Circumference (MAC): indicator of lean body mass. Measurement of fat, muscle and bone at the mid upper arm
C. Bioelectrical impedance: measurement of lean body mass based on the principle that bioelectrical conductance of fatty tissue is lower than the conductance of fat-free tissue
D. Hydrodensitometry: based on the principle that fat-free mass has a higher density than fat. Fat density can be estimated by comparing body weight in air vs weight in water

V. Biochemical Measurements of Malnutrition
A. Delayed type hypersensitivity—depressed cell-mediated immune response in children with protein-calorie malnutrition results in delayed or absent response to intradermal antigens
   1. Decreased reactivity to Candida albicans skin testing
   2. Seen in moderate to severe malnutrition
   3. Associated with increased surgical complications
B. Lymphopenia
   1. Thymic atrophy and a decrease in T-cell numbers have been observed in malnourished children
C. Nitrogen balance—reflection of the adequacy of dietary protein
   1. Negative nitrogen balance may indicate inadequate protein intake
   2. Negative nitrogen balance may indicate increased catabolic stress, leading to lean mass breakdown. High nitrogen losses can be seen in burn patients and in those with inflammatory bowel disease for example
   3. Positive nitrogen balance can be seen in anabolic states (e.g., states of growth and tissue repair). A goal of zero balance is used when a patient has adequate visceral protein stores.
D. Visceral protein levels
   1. Blood concentrations of visceral proteins (C-reactive protein, fibrinogen, ferritin, ceruloplasmin, alpha-1-antitrypsin, albumin, prealbumin, retinol binding protein, transferrin and alpha-1-acid glycoprotein) synthesized by the liver can be a reflection of protein nutrition. Decreased levels may reflect decreased stores of amino acid precursors and/or visceral mass. Levels may vary with infection or catabolic illnesses
      a. Blood concentrations of the following visceral proteins increase with catabolic stress, such as fever or infection: C-reactive protein, fibrinogen, ferritin, ceruloplasmin, alpha-1-antitrypsin and alpha-1-acid glycoprotein
      b. Blood concentrations of the following visceral proteins decrease with catabolic stress: albumin, prealbumin, retinol binding protein and transferrin
   2. Albumin is the most abundant serum protein. Half-life is 20 days
   3. Prealbumin is a more useful measurement of protein recovery. Half-life is 2 days
   4. Retinol Binding Protein (RBP): rapid response to protein-energy depletion and repletion. Half-life is 12 hours. RBP is metabolized by the kidney; high levels may develop in renal failure
   5. Transferrin: binds iron for delivery to the tissues. Half-life is 8 days. Increased concentrations seen in iron deficiency anemia, pregnancy, and with oral contraceptive use. Decreased transferrin levels found in iron overload, anemia of chronic disease, and steroid therapy
E. Total energy expenditure (TEE)
   1. TEE is the sum of the energy required for BMR (REE) + energy required for activity (EER) + energy required for growth + energy lost in urine and stool
   2. Estimate the energy required for basal metabolic rate (REE) by the Harris Benedict Equation in adolescents and adults—see below
   3. Basal Energy Expenditure for Children (see Table 2)
Table 2. Schofield Equations for Basal Energy Expenditure for Children

<table>
<thead>
<tr>
<th>Age</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–3 year</td>
<td>((0.167 \times \text{wt}) + (15.174 \times \text{ht}) - 617.6)</td>
<td>((16.252 \times \text{wt}) + (10.232 \times \text{ht}) - 413.5)</td>
</tr>
<tr>
<td>3–10 years</td>
<td>((19.59 \times \text{wt}) + (1.303 \times \text{ht}) + 414.9)</td>
<td>((16.969 \times \text{wt}) + (1.618 \times \text{ht}) + 371.2)</td>
</tr>
<tr>
<td>10–18 years</td>
<td>((16.25 \times \text{wt}) + (1.372 \times \text{ht}) + 515.5)</td>
<td>((8.365 \times \text{wt}) + (4.65 \times \text{ht}) + 200)</td>
</tr>
</tbody>
</table>

4. Resting energy expenditure (REE): Used as an approximation of BMR. The difference between BMR and REE is thought to be <10%. Indirect calorimetry is used to measure REE.

5. Estimated Energy Requirement (EER): Average dietary energy intake required to maintain current weight and activity in healthy individuals with normal physical activity.

Recommended Reading


I. Incidence
10% of children seen in the primary care setting have signs of growth failure. The etiology is most often multifactorial. Laboratory screening is typically low yield with the majority of diagnoses coming from a complete history and physical exam.

II. Overview/Epidemiology
A. 1%–5% of referrals to children’s hospitals are for growth failure
B. 15%–30% of children in inner-city emergency departments have signs of growth failure
C. Occurs more frequently in children living in poverty
D. ~20%–33% of cases are undiagnosed

III. Definition
A. The term “failure to thrive” is falling out of favor. Many advocate for using less pejorative terms, such as growth failure, poor weight gain or undernutrition
B. Growth failure is multifactorial in origin. It is the final common pathway of many medical, psychosocial and environmental processes
C. Current definition for children younger than 2–3 years of age
   1. Weight <3rd/5th percentile for age on more than one occasion
   2. Weight <80% of ideal weight for age
   3. Weight crosses two major percentiles on standardized growth curve over time

IV. Pathogenesis
A. Organic vs Nonorganic vs Mixed
   1. Organic: attributed to major/chronic illness
   2. Nonorganic: environmental/psychosocial factors
   3. Mixed: combination of illness and psychosocial factors
B. Inadequate Caloric Intake
   1. Maternal/infant dysfunction resulting in poor intake
   2. Mechanical problems impairing infant feeding
      a. Sucking/swallowing dysfunction
      b. Inappropriate feeding technique
   3. Inappropriate diet
   4. Insufficient lactation in mother
   5. Economic factors
C. Inadequate Caloric Absorption
   1. Malabsorption
      a. Cystic fibrosis or other pancreatic insufficiency
      b. Milk allergy with intestinal damage
      c. Lactose intolerance usually does not result in calorie deprivation in young infants
      d. Celiac disease
      e. Chronic liver disease with fat malabsorption
   2. Vomiting that produces excess losses or prevents adequate intake
   3. Inflammatory bowel disease may cause malabsorption ± increased expenditure due to inflammation and anorexia with inadequate intake
   4. Chronic renal disease
D. Excessive Caloric Expenditure
   1. Hyperthyroidism
   2. Congenital/acquired cardiac disease
   3. Cystic fibrosis, bronchopulmonary dysplasia and other pulmonary disease
   4. Cerebral palsy and other hypertonic muscle disease
   5. Malignancy
   6. Metabolic disease and mitochondrial disease with abnormal intermediary energy metabolism

V. Diagnosis
   A. History
      1. Feeding behaviors
      2. Dietary history—detailed!
      3. Social history—documented observations of maternal/child interactions and parental/physician interactions
      4. Thorough review of systems to detect red flags for organic disease
      5. Physical exam
         a. Plot weight, height and head circumference
         b. Wasting defined as decreased weight for height signals acute malnutrition
         c. Stunting defined as decreased height for age signals chronic malnutrition

VI. Evaluation
   A. Only 1.4% of laboratory studies performed in evaluating children with growth failure are useful diagnostically. Most diagnoses are suggested by history and physical examinations
   B. Usual screening examinations include:
      1. CBC, basic metabolic panel, liver functions
      2. Urine analysis
      3. Stool examination for blood, fat and infection
   C. Occasionally useful screening tests depending on age: thyroid panels, celiac screening and sedimentation rate
   D. Document intake with 2–3-day diet record
   E. Monitor growth measurements over time

VII. Therapy/Treatment
   A. Determine contributing factors and address them
   B. Create positive interactions and a positive feeding environment
   C. Dietary supplementation
      1. Increase caloric density for infants
      2. Add high-calorie foods such as sour cream, butter, peanut butter, cheese for older children
   D. Behavior Modification
      1. Reduce snacking/grazing
      2. Turn off TV while eating
      3. Eat as a family
   E. Multiple vitamins with iron and zinc may be needed in children with inflammatory disease and malabsorption syndromes
   F. Appetite stimulants: zinc and cyproheptadine have been used, with no proven long-term effect
   G. Monitor for refeeding syndrome in severely malnourished children (see section on Malnutrition)
   H. Provide calories for catch-up growth
      1. Defined as weight gain needed to return child to previous normal growth trajectory and percentiles
      2. Catch-up weight gain is 2–3x greater than normal rate for age
      3. Estimate ~150 kcal/kg/day for child aged 0–1 years to induce catch-up growth
      4. Severe FTT may need >200 kcal/kg for catch-up growth
      5. Usually some acceleration of weight gain occurs after 2 days–2 weeks of increased calories
      6. 6–12 months needed to restore height and weight to genetically appropriate level
Recommended Reading


I. Incidence
44% of children presenting to gastroenterology (inpatient and outpatient combined) have evidence of malnutrition, growth failure, or are overweight. Of the affected children, 20% are acutely malnourished and 31% are chronically malnourished. Infants and toddlers are at the highest risk for malnutrition. Chronic malnutrition appears to be equally distributed amongst all pediatric age groups. Acute malnutrition is seen more often in adolescents.

II. Indications for Nutritional Assessment
A. Any child with height-for-age <10th percentile
B. Child <2 years with weight-for-height <15th percentile. Child >2 years with BMI <15th percentile
C. Child >2 years with BMI >85th percentile (obesity)
D. Failure of appropriate growth during a 6-month to 1-year interval
E. Child >2 years with height velocity <5 cm/year (chronic malnutrition)
F. Prepubertal weight velocity <1 kg/year or pubertal weight velocity <1 kg/6 months (acute malnutrition)
G. Hospitalized children or children with chronic medical conditions, especially recurrent febrile illness or malignancy (the more complex the medical or surgical problem, the higher risk of nutritional disorders)
H. Children with very limited dietary habits, feeding behavior issues, and abnormal activity levels
I. Children who are taking medication, developmentally delayed, anemic, allergic or intolerant to certain foods, on a special diet, formula, prescribed or self-imposed fad diet, using supplemental foods or vitamins, difficult to feed or have dental problems, not ambulatory, sedentary or overly active

III. Goal of Nutritional Assessment
A. To prevent nutritional disorders and the increased morbidity and mortality that accompany them

IV. Components of Nutritional Assessment
A. Dietary, medical and medication history
B. Physical examination
C. Growth, anthropometric and body composition measurements
D. Laboratory tests
E. Intervention and monitoring

V. Types of Nutritional Disorders
A. Stunting (low height for age) is caused by long-term insufficient nutrient intake and frequent infections. Usually occurs before the age of 2. Also referred to as chronic malnutrition. Cognitive effects are largely irreversible
B. Wasting (weight for height more than 2SD below the mean) is caused by acute significant food shortage and/or disease. Also referred to as acute malnutrition
C. Overweight (BMI 85th–95th percentile for age) or obesity (BMI >95th percentile for age)
### Table 1. Classifying Malnutrition

Guidelines adapted from JC Waterlow and AA Kanawati (1970s):

<table>
<thead>
<tr>
<th>Method</th>
<th>0 Normal</th>
<th>1 Mild</th>
<th>2 Moderate</th>
<th>3 Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight-for-height, % expected</td>
<td>≥90</td>
<td>&lt;90</td>
<td>&lt;80</td>
<td>&lt;70</td>
</tr>
<tr>
<td>Height-for-age, % expected</td>
<td>≥95</td>
<td>&lt;95</td>
<td>&lt;90</td>
<td>&lt;85</td>
</tr>
<tr>
<td>Mid-arm-circumference/fronto-occipital-circumference</td>
<td>≥0.31</td>
<td>&lt;0.31</td>
<td>&lt;0.28</td>
<td>&lt;0.25</td>
</tr>
</tbody>
</table>

Guidelines from the World Health Organization:

<table>
<thead>
<tr>
<th></th>
<th>Moderate</th>
<th>Severe (type)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symmetrical edema</td>
<td>No</td>
<td>Yes (edematous malnutrition)</td>
</tr>
<tr>
<td>Weight-for-height</td>
<td>−3 ≤ SD-score &lt; −2 (70%–79%)</td>
<td>SD-score &lt; −3 (&lt;70%) (severe wasting)</td>
</tr>
<tr>
<td>Height-for-age</td>
<td>−3 ≤ SD-score &lt; −2 (85%–89%)</td>
<td>SD-score &lt; −3 (&lt;85%) (severe stunting)</td>
</tr>
</tbody>
</table>

SD score = deviation of the value for an individual from the median value of the reference population, divided by the standard deviation of the reference population

### VI. Types of Malnutrition

A. Severe protein and calorie malnutrition without nutritional edema = **marasmus**

B. Severe protein malnutrition with nutritional edema = **kwashiorkor**

### VII. Biochemical, Hematologic and Radiologic Evaluation of Malnutrition

A. Laboratory evaluation for specific diseases as directed by the history and physical

B. Hemoglobin and red blood cell indices

1. May identify children with nutritional deficiencies of iron, folate or vitamin B₁₂ or with anemia of chronic disease

2. Iron deficiency anemia (hypochromia and microcytosis) is the most common nutritional deficiency in children, presents with low serum iron, high serum iron-binding capacity, low serum ferritin

3. Causes of microcytic anemia include deficiencies of iron, vitamin E, lead toxicity and _Thalassemia minor_

4. Ferritin measures body iron stores, also an acute phase reactant

5. Macrocytic anemia: suggests deficiency of folic acid or vitamin B₁₂ especially when hypersegmented neutrophils are seen

6. Anemia of chronic disease is normochromic, normocytic and hypoproliferative. May see low iron, low iron-binding capacity and normal to increased ferritin

C. Prealbumin and albumin

1. Prealbumin: indicator of adequacy of short-term nutrition, synthesized in liver, half-life is 2 days. Falls rapidly with poor dietary intake, rises within 10 days of adequate nutrition. Falls in the presence of infection. Threshold defining low levels is 13 mg/dL in children and 4 mg/dL in neonates

2. Albumin: indicator of adequacy of long-term nutrition, synthesized in liver, half-life is 14–20 days, so reflects intake in past 3 weeks. May take up to 3 weeks to normalize following initiation of nutritional therapy

D. Effects of nutritional disorders on cellular immunity: low lymphocyte count and depressed delayed-type hypersensitivity testing

E. Vitamin levels: fat-soluble vitamins A, D, E and K may be low in malabsorptive disorders, such as cystic fibrosis, cholestasis, inflammatory bowel disease and celiac disease

F. Specific mineral levels may be useful in certain types of chronic illness. Example: zinc deficiency in IBD, copper deficiency in patients on PN without mineral supplementation
G. Serum potassium and phosphorus should be monitored during refeeding of chronically malnourished patients. Intracellular ion shifts lead to hypokalemia and hypophosphatemia, which may cause serious cardiac arrhythmias and muscle weakness.

H. Radiologic evaluation includes bone age in children with short stature, bone density for those at risk of osteopenia, e.g., IBD, anorexia nervosa, cholestasis, cystic fibrosis.

**VIII. Management of Acute Malnutrition**

A. First response: in a resource-rich environment, consider chronic condition or illness. In a resource-poor environment, malnutrition secondary to inadequate dietary intake is most likely.

B. Decision to treat in hospital or home: depends on clinical presentation and resources available. If uncomplicated, manage at home. If complicated, proceed with facility-based care.

1. Children who have severe wasting or symmetrical edema involving at least the feet are severely malnourished and should be admitted to a facility (see WHO guidelines for details).

2. Clinical features associated with complicated malnutrition: fever related to systemic infection, respiratory distress, heart failure, electrolyte derangements, marked anorexia, anemia, profuse diarrhea and shock.

C. Acute moderate malnutrition: add a nutrient-rich supplemental food that provides the RDA of all micronutrients and 75 kcal/kg/day.

D. Uncomplicated acute severe malnutrition: manage at home with ready-to-use therapeutic food, provide 175 kcal/kg/day.

   1. Examples of therapeutic foods: F-75 and F-100. Both contain dried skimmed milk, sugar, cereal flour, vegetable oil, mineral mix, vitamin mix and water.

E. Complicated acute severe malnutrition: inpatient treatment with liquid food every 2 hours, 100 kcal/kg/day, treat for sepsis and monitor for shock. Do not give IV fluids except in profuse diarrhea or hypovolemic shock, because IV fluids can stress the organs and precipitate heart failure.

F. Causes of death in severe malnutrition: hypoglycemia, hypothermia, cardiac failure from overhydration and electrolyte imbalance, and infection.

G. Standardized protocol based on WHO guidelines: slower rehydration, avoidance of IV fluids, routine use of antibiotics, immediate feeding, greater use of tube feeding, supplementation of potassium, magnesium and micronutrients. Slow advancement to prevent refeeding syndrome (see section on Eating Disorders).

**Recommended Reading**


I. Incidence
Childhood obesity is epidemic in the United States. The number of affected, the number of affected children continues to increase. There are multiple factors involved, but the majority of cases can be explained by excess calorie intake and inadequate expenditure.

II. Epidemiology
A. Obesity defined as BMI >95% for age using CDC growth charts from 2000
   1. 10.4% in 2–5 years old
   2. 19.6% in 6–11 years old
   3. 18.1% in 12–19 years old
C. Hispanic boys of all age groups have higher risk of obesity (OR 1.80) than non-Hispanic white boys
D. Non-Hispanic black girls have higher risk of obesity (OR 1.70) than non-Hispanic white girls

III. Gastrointestinal Complications
A. Non-Alcoholic Fatty Liver Disease (NAFLD)
   1. Single-center study of autopsy specimens estimates NAFLD prevalence of 38% in obese children
   2. Progression to hepatic dysfunction in childhood is rare, but fibrosis (67%) and steatohepatitis (30%) are common
B. Functional abdominal disorders
   1. Higher prevalence of obesity in children with functional GI disorders than in controls
C. Cholelithiasis
   1. A particular risk in women with extreme obesity (up to 7-fold increase in risk in adult women with extreme obesity)
D. Abnormal lipid profile
   1. Defined as any combination of the following: elevated total cholesterol, elevated low-density lipoprotein cholesterol (LDL-C), elevated triglyceride or low high-density lipoprotein cholesterol (HDL-C)
E. Pancreatitis
   1. Obesity is an independent risk factor for severity of pancreatitis in adults, perhaps due to circulating inflammatory adipocytokines

IV. Non-gastrointestinal complications
A. Insulin resistance and Type 2 Diabetes Mellitus (Type 2 DM)
   1. Impaired glucose tolerance in 21% and Type 2 DM in 4% of asymptomatic obese adolescents
   2. Risk of obstructive sleep apnea increases 3.5-fold for every standard deviation increase in BMI z-score in adolescents with snoring
B. Hypertension—prevalence is 34% in children with BMI >95% for age
C. Polycystic Ovarian Syndrome: 30%–70% of women with PCOS are obese
D. Slipped Capital Femoral Epiphysis (SCFE)
   1. Increased mechanical load across proximal femoral physis
   2. Increasing incidence over last 2–3 decades
   3. BMI in SCFE is higher than in general population
E. Blount disease (bowing of tibia)
   1. Disordered ossification of proximal tibial physis; can lead to limb shortening. Obesity produces excessive compressive force on physis, inhibiting growth
F. Idiopathic Intracranial Hypertension (Pseudotumor Cerebri)
   1. Increased intracranial pressure of unknown cause can lead to permanent visual loss
   2. Weight loss associated with improvement in symptoms

G. Psychological problems
   1. A meta-analysis in adults showed that obesity increases risk of depression (OR 1.55)
      Also, depression is predictive of developing obesity (OR 1.58)

V. Etiology
   A. Obesity is almost always multifactorial, including genetic, epigenetic, environmental and
      behavioral factors
      1. The strongest genetic association with obesity are variants in the FTO gene (fat mass
         and obesity-related gene). These variants only explain 0.5% of variance in BMI
   B. Syndromic and Monogenic Forms of Obesity
      1. Monogenic (rare): leptin, leptin receptor, melanocortin 4 receptor
      2. Syndromic: Prader-Willi syndrome, pseudohypoparathyroidism type 1A, Bardet-Biedl
         syndrome

VI. Management
   A. Workup should include thyroid studies, fasting plasma glucose concentration, serum insulin
      levels, serum lipid concentrations and serum aminotransferase levels
   B. Nutritional and behavioral management
      1. Portion reduction
      2. Avoidance of sugar-containing beverages, restaurant meals and fast food,
         calorie dense snacks and eating in front of television
      3. Decrease time spent in front of television and increase activity levels
   C. Drugs
      1. Orlistat: lipase inhibitor reduces fat absorption by 30%
         a. Modest weight loss (<10%) in placebo-controlled trial
         b. Side effects: steatorrhea, abdominal pain, flatulence
      2. Metformin: reduces hepatic glucose production and increases insulin sensitivity
         a. Modest weight loss (<10%) in multiple trials
      3. Sibutramine: centrally acting serotonin and norepinephrine reuptake inhibitor
         a. Pooled results from four studies in adolescents showed mean BMI reduction of
            2.2 kg/m²
         b. Withdrawn from use in U.S. in 2010 because of risk of heart attack and stroke
            in adults
   D. Weight Loss Surgery (WLS) (bariatric surgery)
      1. Patient selection: recent expert panel recommendations:
         a. Adolescents with BMI ≥35 and one of the comorbidities below
            1) Type 2 diabetes mellitus
            2) Moderate-to-severe obstructive sleep apnea
            3) Pseudotumor cerebri
            4) Severe steatohepatitis
         b. In the absence of complications, only adolescents with BMI >40 are candidates
            for weight loss surgery
         c. Compliance with medical treatment and monitoring must be demonstrated
            prior to WLS
         d. Patients must be Tanner stage IV or V
         e. Skeletal maturation of 95% if diversion procedure is planned
      2. Laparoscopic Roux-en-Y Gastric Bypass (RYGB)
         a. Percent decline in BMI at 1 year postoperatively is 36%–37%
         b. Metabolic improvement (insulin sensitivity) occurs independent of weight loss
            and BMI improvement for unclear reasons
         c. Immediate postoperative complications
            1) Bowel obstruction
            2) Wound infection
            3) Dehydration
            4) Intestinal leakage
         d. Micronutrient deficiencies post-RYGB: iron, vitamin D, vitamin B₁₂,
            calcium and thiamine
3. Laparoscopic Gastric Band (Lap Band)
   a. Randomized trial comparing gastric band to lifestyle intervention in obese adolescents showed significantly greater weight loss and improvement in insulin sensitivity in lap band after two years
   b. Multiple studies show persistence of weight loss after lap band
   c. Reoperation (band removal, band replacement or adjustment) occurs in 10% or more of adolescent patients
   d. Risk of vitamin deficiency is less than that after RYGB

Recommended Reading


8H. Normal Digestion and Absorption

Carolina S. Cerezo, MD

I. Process
Digestion and absorption of food is a complex process that begins in the mouth and continues through to the colon with water and salt absorption. Fats, carbohydrates and protein all have specialized digestion and absorption processes. These processes evolve from the neonate to child, reflecting the dietary intake at different stages.

II. Phases of Digestion and Absorption
A. Cerebral:
1. Initial phase of the digestive process
2. Salivary and gastric secretory responses are triggered by sight, smell and thought of food. Mediated by autonomic nervous system via the vagus nerve
B. Oral:
1. Limited digestion of starch by salivary amylase
2. Lingual lipase produced by von Ebner glands on the dorsum of the tongue provide up to 50% of total lipolytic activity in neonates
C. Gastric:
1. Pepsin initiates protein digestion by preferentially cleaving hydrophobic and aromatic amino acids and may account for up to 20% of proteolysis
2. Gastric lipase does not require bile or colipase for maximal activity, and may provide up to 30% of lipolysis
D. Intestinal: duodenum initially enhances gastric activity to process chyme in the stomach
1. As chyme arrives in the duodenum, gastric secretion and motility are suppressed to allow for intestinal digestion and absorption

III. Satiety Signals (see Table 1)
Satiety signals are relayed to the hindbrain indirectly via the vagus nerve and direct to the hindbrain via mediators in the blood.

<table>
<thead>
<tr>
<th>Mediator</th>
<th>Source</th>
<th>Receptor</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCK (Cholecystokinin)</td>
<td>I cells in the mucosal epithelium of the small intestine</td>
<td>CCK receptors in CNS</td>
<td>Suppresses appetite by inhibition of gastric emptying and secretion</td>
</tr>
<tr>
<td>GRP (Gastrin Releasing Peptide)</td>
<td>Secreted by post ganglionic vagal fibers in the antrum</td>
<td>Antral G-cells</td>
<td>Gastrin induces satiety by increasing gastric acid secretion and delaying gastric emptying</td>
</tr>
<tr>
<td>APO IV (apolipoprotein a-IV)</td>
<td>Intestinal mucosa</td>
<td>CNS receptors</td>
<td>Centrally mediated appetite suppression in response to fat absorption</td>
</tr>
<tr>
<td>Leptin</td>
<td>Adipocytes</td>
<td>Hypothalamus</td>
<td>Decrease appetite</td>
</tr>
<tr>
<td>PYY (peptide tyrosine-tyrosine)</td>
<td>L cells in ileum and colon</td>
<td>NPY (neuropeptide Y) receptors in the CNS and ANS</td>
<td>Reduces appetite by slowing gastric emptying and inhibition of pancreatic secretion</td>
</tr>
<tr>
<td>PP (pancreatic polypeptide)</td>
<td>Pancreatic endocrine cells (F cells)</td>
<td>PP receptors in pancreas, GI tract and CNS</td>
<td>Inhibits pancreatic exocrine secretion, gallbladder contraction and gut motility</td>
</tr>
</tbody>
</table>
Table 1. Satiety Signals

<table>
<thead>
<tr>
<th>Mediator</th>
<th>Source</th>
<th>Receptor</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP (glucagon-like peptide)</td>
<td>Ileal L cells</td>
<td>GLP-1 receptors in the pancreas</td>
<td>Inhibits gastric motility; contributes to satiety by delaying absorption of carbohydrates</td>
</tr>
<tr>
<td>Oxyntomodulin</td>
<td>Oxyntic cells in the colon</td>
<td>GLP-1 and glucagon receptor in the pancreas</td>
<td>Suppresses appetite by binding to the GLP1 receptors</td>
</tr>
<tr>
<td>Ghrelin “hunger hormone”</td>
<td>D cells in the stomach and epsilon cells in pancreas</td>
<td>Ghrelin receptor in the hypothalamus and pituitary gland</td>
<td>Stimulates hunger and growth hormone secretion</td>
</tr>
</tbody>
</table>

IV. Gastric Emptying

A. Gastric factors controlling gastric emptying are:
   1. Rate of gastric emptying is proportional to the volume of chyme
   2. Gastric distension triggers increased gastric motility through direct effects on gastric stretch receptors and via the vagus and intrinsic nerves of the stomach wall

B. Duodenal factors controlling gastric emptying are:
   1. Particle size/consistency – pylorus retains particles >2 mm
   2. pH – acid pH of antral contents delays gastric emptying
   3. Osmolality – hypertonicity of gastric contents stimulates osmoreceptors and chemoreceptors in the duodenum that delay gastric emptying
   4. Increased fat content of chyme slows emptying
   5. Duodenal mucosal receptors for fatty acids, amino acids and carbohydrates are triggered by increase in size or energy density (not osmolality) of a meal and lead to increased emptying and rate of delivery
   6. Ileal brake – unabsorbed nutrients in the ileum and colon stimulate secretion of hormones PYY, GLP-1 and GLP-2. These slow gastric emptying

V. Effects of Chyme in the Duodenum

A. Serotonin, released from intestinal enterochromaffin cells and nerve terminals of the enteric nervous system (ENS) mediate CCK and secretin secretion into portal circulation, where they bind to receptors in the gallbladder and pancreas
   1. CCK promotes gall bladder contraction and pancreatic enzyme, water and ion secretion
   2. Secretin stimulates pancreatic enzyme and bicarbonate secretion

B. Exocrine pancreatic secretion is controlled by coordination of cephalic (vagus), gastric (acid, pepsin and gastric emptying) and intestinal (CCK/secretin) mechanisms

C. Enteropeptidase (enterokinase) secreted from duodenal crypts of Lieberkuhn, in response to chyme, activates pancreatic trypsinogen to trypsin. Trypsin activates other pancreatic enzymes

D. Ingestion of a meal stimulates water and salt secretion in the jejunum to maintain fluid state of luminal contents

E. Intestinal motor response is altered in the presence of distention, and pH and osmolality of chyme. Repetitive pattern of interprandial resting motor activity seen in fasting changes to the disrupted/disordered pattern post-prandially to allow mixing of luminal contents

VI. Intestinal Conservation and Recycling

A. Acid-base balance is maintained by neutralization of gastric acid
B. Nitrogen is absorbed from metabolized digestive enzymes and mucous
C. Bile acids are preserved via active reabsorption from the ileum and uptake by the liver
D. Water and salt are preserved via colonic reabsorption
E. Dietary fibers are broken down to short-chain fatty acids by colon bacteria and absorbed in the colon
VII. Fat Digestion/Absorption

A. Lipids supply about 40% of adult energy requirements

B. Polyunsaturated fatty acids (PUFA), linoleic and linolenic acid, are not synthesized by humans and are essential

C. Most lipids absorbed in the upper 2/3 of the jejunum

D. Soluble dietary fiber reduces fat absorption by binding to bile acids

E. Steps in fat digestion
   1. Hydrolysis of triglycerides liberates fatty acid, glycerol and some di- and monoglycerides
   2. 20%-30% occurs in stomach via gastric lipase and lingual lipases at pH optimum 4.5, and 70%-80% in the duodenum via pancreatic lipase and co-lipase at pH optimum >6.0
   3. Optimal function of pancreatic lipase also requires bile salts
   4. Products of lipolysis are stabilized (emulsified) by phospholipids and bile salts in micelles. Hydrophobic region of bile salts forms the core of micelle, with hydrophilic region to the exterior
   5. Phosphatidylcholine (lecithin), the major dietary phospholipid, is hydrolyzed by pancreatic phospholipase A2
   6. Cholesterol esters are hydrolyzed by carboxyl ester lipase or pancreatic cholesterol esterase in the presence of bile salts and calcium

F. Fat absorption
   1. Transfer of fatty acids, monoglycerides and phospholipid across the brush border membrane of enterocytes is by passive diffusion of micelles and transfer to lymphatic vessels in the core of the villus
   2. Other lipid containing particles transfer lipids to the mucosa via formation of liquid crystals on the surface of the shrunken emulsion droplet. It is not clear how significant this mechanism of absorption is
   3. The unstirred water layer on the luminal surface of epithelial cells may be rate-limiting for uptake of long-chain fatty acids, but is not a factor in absorption of short- and medium-chain fatty acids
   4. Transfer of LCFA across the brush border membrane
      a. Extracellular: long-chain fatty acid (LCFA) binds to fatty acid transport protein complex on the enterocyte surface
      b. Intracellular: LCFAs are coupled to Coenzyme A by LCFA acyl Coa synthetase to prevent efflux from the enterocyte
      c. Fatty acid-binding protein acts as a cytoplasmic buffer for incorporation of LCFA into the cell

G. Intracellular processing of lipids
   1. Absorbed intracellular fatty acids bind to fatty acid-binding proteins for transport to the endoplasmic reticulum (ER)
   2. In the ER, triglyceride is resynthesized by two processes
      a. Monoglyceride pathway in which triglycerides are resynthesized from absorbed fatty acids and monoglycerides
      b. Microsomal triglyceride transfer protein (MTP) transfers resynthesized TG, phospholipids and cholesterol to apolipoproteins A1 A4 and B48. Deficiency of MTP is the cause of abetalipoproteinemia
      c. Triglycerides and phospholipids are synthesized via the α-glycerophosphate pathway, in which α-glycerophosphate is acylated with formation of phosphatidic acid and triglyceride (or phospholipid)
      d. Absorbed cholesterol is transported as esterified cholesterol almost exclusively by the lymphatic system
      e. After resynthesis, TG, cholesterol, cholesterol esters and phospholipids are exported as chylomicrons and very low-density lipoproteins (VLDL)
      f. During fasting, VLDL is the major triglyceride-containing lipoprotein. After feeding, chylomicrons predominate

H. Disorders of fat absorption (See Table 2)
### Table 2. Disorders of Fat Absorption

<table>
<thead>
<tr>
<th>Stage of Fat Digestion/Absorption</th>
<th>Defect</th>
<th>Clinical Condition</th>
<th>Findings, Diagnosis</th>
</tr>
</thead>
</table>
| **Emulsification/Formation of Micelles** | Defect in fatty acid ionization                      | Hyperacidity, ie, Zollinger-Ellison syndrome | Gastrinomas in pancreas or duodenum  
Increased serum gastrin  
Rare in children                                 |
| **Hydrolysis**                   | Deficiency of pancreatic lipase, colipase or bicarbonate ion | Pancreatic insufficiency | Fecal elastase <200 mcg/g  
Cystic fibrosis  
Isolated lipase and colipase deficiency  
Schwachman syndrome  
Johanson-Blizzard syndrome  
Pearson syndrome | Deficiency of fatty acid ionization  
Hyperacidity, ie, Zollinger-Ellison syndrome  
Gastrinomas in pancreas or duodenum  
Increased serum gastrin  
Rare in children  
Pancreatic insufficiency  
Fecal elastase <200 mcg/g  
Cystic fibrosis  
Isolated lipase and colipase deficiency  
Schwachman syndrome  
Neutropenia and pancreatic insufficiency  
Johanson-Blizzard syndrome  
Dysmorphic facies and pancreatic insufficiency  
Pearson syndrome  
Sideroblastic anemia, mitochondrial cytopathy and pancreatic insufficiency  
Pancreatic insufficiency  
Fecal elastase <200 mcg/g  
Cystic fibrosis  
Isolated lipase and colipase deficiency  
Schwachman syndrome  
Neutropenia and pancreatic insufficiency  
Johanson-Blizzard syndrome  
Dysmorphic facies and pancreatic insufficiency  
Pearson syndrome  
Sideroblastic anemia, mitochondrial cytopathy and pancreatic insufficiency |
| **Solubilization**               | Deficiency of bile salts                             | Biliary obstruction | Cholestasis, increase direct bilirubin, serum bile acids, e.g., TPN cholestasis, Biliary atresia, Alagille syndrome, PFIC  
Impaired synthesis | Deficient or missing serum bile acids  
Resection of the terminal ileum, e.g., short bowel syndrome, post-surgery in Crohn disease, gastric bypass surgery  
Small bowel bacterial overgrowth, blind loop syndrome deconjugates bile acids  
Positive hydrogen breath test |
| **Mucosal Cell**                 | Enteropathy                                          | Celiac disease     | Histology: villous atrophy  
Giardia lamblia  
Deficiency of lipoproteins | Histology: villous atrophy  
Giardia lamblia  
Abetalipoproteinemia  
Anderson disease | Histology: villous atrophy  
Giardia on biopsy, watery fatty stools + O/P stool, + Giardia antigen in stool  
Deficient or absent plasma LDL and apo B, Histology: lipid-filled enterocytes  
Deficiency of apo-B48, autosomal recessive |
| **Chylomicron Transport**        | Lymphatics obstruction of malformation              | Lymphangiectasia    | Distorted villi with ectatic lymphatics  
Hennekam syndrome  
Protein-losing enteropathy s/p Fontan operation | Distorted villi with ectatic lymphatics  
Lymphangiectasia and mental retardation  
Increased fecal alpha 1-antitrypsin  
Post small bowel Tx | Distorted villi with ectatic lymphatics  
Lymphangiectasia and mental retardation  
Increased fecal alpha 1-antitrypsin  
Post small bowel Tx |

### VIII. Carbohydrate Digestion/Absorption

A. Carbohydrate is the major source of calories in humans. Half of the digestible carbohydrate in western diets is starch  
B. Amylose (linear α 1, 4 links) and amylopectin (branched α 1,6 links) are long chain polymers of glucose  
C. Other sources of carbohydrate: milk (lactose), cells of fruits and vegetables (fructose, sucrose and glucose), purified cane/beets (sucrose)  
D. Sorbitol is a sugar alcohol with slow rate of absorption and minor impact on blood sugar  
E. Glycogen is the major storage form of carbohydrate in animals with a structure similar to amylose  
F. Non-starch polysaccharides are unavailable, e.g., cereals, peas, beans, carrots, peanuts, pectin, gums, alginates and lignin  
G. Cellulose and hemicellulose are resistant to human enzymes
H. Fiber delays the absorption of sugars and curtails insulin response to carbohydrate load

I. Intraluminal carbohydrate digestion
   1. Salivary amylase activity promoted by slow chewing, prolonging the oral phase
   2. Salivary amylase rapidly inactivated by gastric acid
   3. Human milk contains amylase
   4. Pancreatic amylase is the major starch hydrolyzing enzyme
   5. Amylases produce oligosaccharides, maltotriose, maltose and alpha limit dextrins (short branched chain oligosaccharides), NOT glucose monomers

J. Brush border membrane hydrolases (see section on Disaccharidase Deficiency)
   1. Lactase: lactose → glucose and galactose
   2. Maltase: alpha 4 linked oligosaccharides → glucose
   3. Sucrase: sucrose → glucose and fructose
   4. Isomaltase (debrancher): alpha limit dextrin and alpha 1,6 and 1,4 → glucose
   5. Trehalase: trehalose (α-linked glucose-glucose found in shrimp, baker’s yeast, mushrooms) → glucose

K. Enterocyte monosaccharide transport:
   1. Monosaccharides are transported by saturable carrier systems in the brush border membrane of the enterocyte in proximal and mid-small intestine
   2. Glucose and galactose are actively transported by sodium glucose co-transporter (SGLT 1)
      a. Active glucose transport is driven by Na⁺ gradient across the apical membrane
      b. Each glucose molecule brings with it 2 Na⁺ ions and 2 accompanying anions. This movement drives water molecules across the BBM to maintain cellular iso-osmolality
      c. Congenital glucose-galactose malabsorption caused by mutations in the SGLT1 gene – severe neonatal diarrhea with carbohydrate-containing feedings
   3. Fructose absorbed via facilitated diffusion uses a carrier protein GLUT5
      a. Fructose minimally metabolized in the enterocyte
      b. Transported across the basolateral membrane by GLUT5 and rapidly metabolized by the liver
   4. Monosaccharides exit epithelial cells by way of the basolateral membrane
      a. Depends on facilitated diffusion mediated by specific carrier: GLUT2 for glucose and GLUT5 for fructose
      b. Fanconi-Bickel syndrome: congenital defect in GLUT2
         1) Patients exhibit tubular nephropathy, fasting hypoglycemia, rickets, stunted growth and hepatomegaly due to glycogen accumulation
      c. 20% of starch is undigested and delivered to the colon, where it is metabolized by colon bacteria to SCFA which provides energy

IX. Protein Digestion/Absorption
   A. Protein makes up 10%–15% of Western diet
   B. Deficiency states are rare even with intakes as low as 0.5 g/kg
   C. Plant protein less digestible than animal protein
   D. Quality of protein depends on amino acid composition. High quality proteins are rich in essential amino acids (AA)
   E. Digestion and absorption of protein is complete with only 3%–5% lost in the stool
   F. Secretory IgA, intrinsic factor and alpha-1-antitrypsin in gut lumen are resistant to proteolysis
   G. Intraluminal digestion of protein
      1. Pepsinogen release from gastric chief cells is stimulated by gastrin, histamine and cholinergic nerves
      2. Pepsin is released from pepsinogen by autoactivation in an acid pH
      3. Enterokinase liberated from epithelial membranes by bile acids activates trypsinogen to trypsin
      4. Trypsin activates other pro-enzymes and trypsinogen
      5. Pancreatic proteases
         a. Endopeptidases (trypsin, chymotrypsin and elastase) cleave peptide bonds
         b. Exopeptidases (carboxy peptidase A and B) remove single amino acids from C-terminus
         c. Final products of intraluminal protein digestion are 30% neutral and basic amino acids (AA) and 70% short peptides (2-6 AA in length)
6. Protein digestion at the brush border
   a. Peptidases are present in gut lumen and epithelium
   b. Peptidases produce free amino acids, di- and tripeptides
   c. Active absorption of peptides at the brush border is more efficient than active absorption of amino acids
   d. Amino acid based formulas have no absorptive advantage over hydrolysates with respect to efficiency of protein absorption
   e. Cystinuria and Hartnup disease have defects in transport of basic and neutral AAs. No protein deficiency state occurs in either condition because peptide absorption is normal

H. Absorption of proteins
   1. Di- and tripeptides utilize a separate transport system from single AAs
   2. Kinetic studies have shown greater absorption rate for peptides than AA
   3. Peptide absorption occurs via
      a. Na⁺-H⁺ exchanger (maintains intracellular alkaline pH) in the BBM
      b. Na⁺-K⁺ ATPase in the basolateral membrane, maintains inside negative membrane potential
      c. Cytoplasmic peptidases prevent intracellular accumulation of absorbed peptides

I. Protein exit from the epithelium
   1. Major mechanisms are active transport and passive diffusion across the basolateral membrane
   2. Glutamine is the major energy source for the enterocyte with NH₃ as byproducts
   3. Basolateral membrane has different transport proteins for AA and peptides
   4. Oligopeptides and AA are released to the portal circulation
   5. Majority of absorbed protein that reaches the portal circulation is in the form of AA

X. Vitamin and Mineral Absorption (See Table 3)

<table>
<thead>
<tr>
<th>Water-soluble Vitamin</th>
<th>Transport Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascorbic acid</td>
<td>Active; sodium dependent at the BBM</td>
</tr>
<tr>
<td>Folic acid</td>
<td>Hydrolysis of dietary polyglutamates at BBM; sodium dependent active transport</td>
</tr>
<tr>
<td>Cobalamin</td>
<td>Binds to R protein from the saliva which is hydrolyzed by pancreatic enzymes in the duodenum; binds to intrinsic factor (IF) in the duodenum; uptake of IF-B₁₂ complex at BBM in the ileum by a specific receptor</td>
</tr>
<tr>
<td>Thiamine</td>
<td>Sodium dependent active transport; absorption includes hydrolytic and phosphorylation steps</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>Absorption includes hydrolytic and phosphorylation steps</td>
</tr>
<tr>
<td>Niacin</td>
<td>?</td>
</tr>
<tr>
<td>Pantothenic acid</td>
<td>?</td>
</tr>
<tr>
<td>Biotin</td>
<td>?</td>
</tr>
<tr>
<td>Pyridoxine</td>
<td>Simple diffusion</td>
</tr>
</tbody>
</table>

A. Fat-soluble Vitamins A, D, E, K are all polar and insoluble lipids
   1. Vitamins A, D and E absorbed via passive diffusion
   2. Vitamin K1 (phytomenadione) absorbed via a carrier-mediated uptake
   3. Vitamin K2 (menaquinone) absorbed by passive diffusion
B. Calcium absorption
   1. Plant phytate, oxalate and fiber bind calcium and reduce its availability
   2. Dietary lactose enhances calcium absorption
   3. Duodenum is major site for active transport (transcellular)
      a. Calcium enters cell via specific channels across the apical membrane and binds with calbindin in the cytoplasm
      b. Maximal transport rate correlates with calbindin concentration regulated by 1, 25-dihydroxyvitamin D3 (rate-limiting step)
      c. Calbindin transports calcium to basolateral membrane, where calcium dependent ATPase drives calcium uphill against the electrochemical gradient
   4. Passive (paracellular) calcium transport occurs throughout the small intestine. The jejunum absorbs calcium faster than the ileum and absorption rates are increased by vitamin D
C. Magnesium absorption
   1. Absorption is greater in the ileum than jejunum
   2. Jejunal absorption increased by vitamin D
   3. Ileal transport by both diffusion and carrier-mediated process
D. Iron absorption
   1. Average iron ingestion in meat eating societies is 20–30 mg/day
   2. Only 10% of dietary iron is absorbed
   3. Most absorption occurs in the proximal small intestine
   4. Ferrous (Fe^{2+}) form is absorbed better than ferric (Fe^{3+}) form, which is highly insoluble and the predominant dietary form
   5. At the BBM, ferric iron reduced to ferrous form before cell entry
   6. Heme iron is transported into the cell by a separate mechanism
   7. Intracellular iron binding proteins transfer iron to basolateral membrane for delivery across cell membrane and subsequent binding to transferrin

XI. The Neonatal Intestine
A. >50% of the calorie requirement is provided by fat in milk (95% in the form of triglycerides)
B. Neonates have low pancreatic lipase activity
C. Transporters for bile salts are not programmed to appear on ileal enterocytes until after weaning
D. Triglyceride digestion mostly by milk derived and gastric lipase
E. Protein digestion is incomplete
   1. Pancreatic proteases do not reach adult levels until after weaning
   2. Trypsin and elastase are present in breast milk
F. Gastric acid and pepsin are secreted at birth and reach adult levels by 3–4 months of age
G. Brush border membrane glucose and amino acid transporters are present in fetal intestine, well before birth, along the entire crypt-villus axis
H. Triglyceride digestion in neonates
   1. Milk triglycerides, packaged in small emulsion droplets, are surrounded by trilaminar membrane that includes phospholipid and proteins (albumin and betalactoglobulin)
   2. Since neonatal pancreatic lipase activity is low, digestion is carried out mostly by gastric lipase produced by the gastric chief cells. This lipase has activity at lower pH (4–6) and releases fatty acids and diglycerides
I. Carbohydrate digestion in neonates:
   1. Minimal need for amylase since the major carbohydrate in milk is lactose
   2. Glucosidases/disaccharidases are present at birth in high concentrations
   3. Starch digestion in first 2–3 months of life relies on salivary amylase, mucosal α-glucosidases and colonic salvage by bacterial fermentation of undigested carbohydrate
J. Protein digestion in neonates:
   1. Pancreatic proteolytic enzymes are secreted at birth but at a slower rate than the adults until weaning
   2. Enterokinase present at birth and capable of activating trypsinogen
   3. Despite immaturity of protein digestion, infants can cope with as much as 3–4 grams of protein per kg body weight of casein
      a. Breast milk proteases (e.g., plasmin) assist in protein digestion
      b. Infant intestine can absorb intact macromolecules
      c. Whole proteins, such as immunoglobulins, are absorbed via pinocytosis and endocytosis

Recommended Reading


**8I. Disaccharidase Deficiency**

Rebecca Cherry, MD, MPH

I. **Disaccharidases—Definition**
Disaccharidases are glycoproteins located in the apical portion of the microvillus membrane of enterocytes. They are responsible for the breakdown of α-glycosidic linkages between monosaccharides allowing for transport across the brush border.

II. **Disaccharidases**
A. Four types
   1. Sucrase-isomaltase – hydrolysis products of sucrose are fructose and glucose
   2. Lactase-phlorizin hydrolase – hydrolysis products of lactose are galactose and glucose
   3. Maltase-glucoamylase – hydrolysis products of maltase activity are glucose and glucose oligosaccharides
   4. Trehalase – hydrolysis product is glucose
B. Symptoms of disaccharidase deficiencies are nonspecific but usually coincide with ingestion of the particular disaccharide and do not occur in the absence ingesting the specific disaccharide.
   1. Nausea and abdominal pain
   2. Vomiting
   3. Diarrhea (both osmotic and fermentative)
   4. Abdominal distension and flatulence

III. **Etiology**
A. Primary genetic
   1. Isolated sucrase deficiency is the most common
   2. Isolated congenital lactase deficiency rare
   3. Multiple disaccharidase deficiency rare
   4. Intestinal biopsy usually appears normal
B. Secondary
   1. Usually a result of intestinal mucosal damage from infection, inflammation, drug toxicity, radiation, celiac disease and malnutrition
   2. Intestinal biopsy may reveal findings leading to specific diagnosis
   3. Multiple disaccharidase deficiency is common in secondary deficiency

IV. **Sucrase-isomaltase (SI) deficiency**
A. Sucrase hydrolyzes α-1,2 and α-1,4 glucosidic bonds in sucrose
B. Isomaltase hydrolyzes α-1,6 bonds in starch/glucose polymers, such as amylopectin (found in wheat and potatoes)
C. Genetics/prevalence
   1. At least 12 mutations known in sucrase-isomaltase gene (chromosome 3q25-q26)
   2. Prevalence is <0.2% of North Americans but 2%–10% of Greenland Eskimos
D. Presentation: see symptoms listed above, also can see growth failure
   1. On enzyme studies: essentially no sucrase activity but can have trace-to-normal isomaltase activity
   2. Symptom severity may be modified by presence of other disaccharidase deficiency, sucrose content of diet, GI motility, colon flora, and age (symptoms generally worse in first 3 years of life)
E. Diagnosis

1. Sucrose hydrogen breath test
   a. 2 g/kg sucrose bolus given orally (up to 50 g)
   b. Increase in breath hydrogen of >20 ppm in 2 hours after ingestion indicates sucrase deficiency
   c. Increase in breath hydrogen is a result of colon bacterial fermentation of unhydrolyzed and unabsorbed sucrose
   d. False negative results occur with abnormal motility and failure to deliver unhydrolyzed disaccharide to the colon in a normal interval
   e. False negative results occur when colon flora is suppressed by antibiotics—no fermentation of unabsorbed disaccharide

2. Disaccharidase activity in duodenal biopsies
3. Oral sucrose tolerance tests not generally used. In SI deficiency, blood glucose rises less than 20 mg/dL above fasting in the hour after oral sucrose administration

F. Treatment

1. Low-sucrose/low starch diet (avoid peas, beets, onions, potatoes, wheat)
2. Lyophilized Saccharomyces cerevisiae provides intact sucrase enzyme
3. Liquid yeast sucrase: sacrosidase (Sucraid™ or Isogest™)

V. Lactase-phlorizin hydrolase (LPH) deficiency

A. Lactase breaks down lactose into glucose and galactose
B. Lactase enzyme is complexed with phlorizin hydrolase, which digests beta-glycosylceramides. Physiologic role in humans unknown

C. Prevalence

1. Adult type hypolactasia occurs in 75% of the world’s population
2. Northwestern Europeans where the lactase gene is an autosomal-dominant have lower rate of hypolactasia
3. Adult type hypolactasia affects 100% of Asians, Alaskan natives and Native Americans
4. Adult type hypolactasia affects from 60%–85% of African Americans
5. Hypolactasia starts to develop in childhood after 4 years of age and may develop as late as adolescence with a decrease in lactase activity to 5%–10% of newborn values
6. Congenital lactase deficiency is rare (autosomal recessive; protein-folding defect, lactase enzyme accumulates in ER)
7. Preterm infants have a relative lactase deficiency which resolves with age
8. Lactase may be inducible by steroids in preterm infants, but not in term infants
9. May also be induced by enterocyte hypoxia and by keratinocyte growth factor (in vitro)
10. In patients with intestinal injury causing secondary disaccharidase deficiency, lactase is usually the first disaccharide affected

D. Presentation

1. Colicky abdominal pain, flatulence, and/or diarrhea
2. Most people with lactase deficiency do not have clinical symptoms of lactose intolerance
3. Symptoms occur usually within 3–4 h of lactose ingestion
4. Symptoms can be worse in the setting of rapid intestinal transit (e.g., IBS)
5. Most people with lactase deficiency can tolerate up to 12 g of lactose (about the amount in 1 cup of milk) without difficulty

E. Diagnosis

1. Breath hydrogen testing after lactose ingestion (see sucrase diagnosis)
2. Small bowel biopsy with direct measurement of lactase activity in tissue
3. Trial of lactose-free diet is adequate for diagnosis in most clinical settings

F. Treatment

1. Low-lactose diet
2. Yeast-derived lactase supplements taken with milk products
3. Supplement Ca and Vitamin D if dairy foods are restricted from the diet
VI. Maltase-glucoamylase
   A. Alternate pathway for starch digestion
   B. Deficiency can lead to starch malabsorption
   C. Roughly 2% of chronic childhood diarrhea may be due to this deficiency
   D. Diagnosed by enzyme activity on small intestinal biopsy
   E. Treatment: avoidance of dietary starches and short glucose polymers

VII. Trehalase
   A. Breaks down trehalose, found in some mushrooms, algae and insects
   B. Deficiency is autosomal recessive
   C. Present in 8% of Greenlanders and essentially no other populations
   D. Treatment: avoidance of trehalose

Recommended Reading


I. Transport Defects
Several rare medical conditions are due to congenital defects in enzyme synthesis, or defects in the transport of electrolytes or nutrients across the bowel wall.

II. Abetalipoproteinemia
A. Defective MTP gene (microsomal triglyceride transfer protein) prevents synthesis of β-lipoproteins. Failure to transport absorbed triglycerides and cholesterol esters into the portal circulation with deficiency of triglycerides and cholesterol esters. Triglycerides and apolipoproteins B-100 and B-48 are important to the formation of VLDLs and chylomicrons
B. Inheritance: autosomal recessive
C. Clinical Manifestations
   1. Profound fat malabsorption in the neonate causes diarrhea, emesis and failure to thrive
   2. Untreated patients develop irreversible neurologic abnormalities starting with loss of deep tendon reflexes (vitamin E deficiency)
   3. Other neurologic problems: retinitis pigmentosa, ataxia and spinocerebellar degeneration
   4. Patients may develop fatty food aversion
D. Diagnosis
   1. Low to absent β-lipoproteins in plasma
   2. Plasma triglyceride concentration <10 mg/dL
   3. Serum cholesterol concentration 25–40 mg/dL
   4. Red blood cell acanthocytosis reflects defects in structural lipids of the red cell membrane
   5. Small bowel surface grossly yellow/white from fat. Biopsies show fat-laden enterocytes in the upper portion of the villus. Electron microscopy shows fat droplets in enterocyte cytoplasm (see Figure 1)
E. Treatment:
   1. Diet low in long-chain triglycerides and cholesterol can effectively reduce steatorrhea
   2. The diet should be supplemented with medium-chain triglycerides that can be directly absorbed into the portal circulation without micellar formation
   3. Fat-soluble vitamin supplementation including high doses of vitamin E to minimize neurologic symptoms

Figure 1. Electron microscopy demonstrating fat droplets in the enterocyte. Red blood cell smear with acanthocytosis due to cell membrane defect from defect in structural lipids. Adapted from Pautler D, Easley D, Pohl JF. Abetalipoproteinemia: Image of the month. JPGN. 2008;46(4):355.
III. Primary Bile Acid Malabsorption
   A. Impairment of bile acid reabsorption caused by defective or absent apical sodium co-dependent bile acid transporter (ASBT) of ileal enterocytes and cholangiocytes
   B. ASBT is essential in the enterohepatic circulation of bile acids, which preserves 95% of the bile acids secreted into the intestine
   C. Inheritance: autosomal recessive
   D. Clinical Manifestations
      1. Secretory diarrhea in infancy is driven by two mechanisms
         a. Fat malabsorption
         b. Stimulation of colonocyte secretion of ions and fluids by unabsorbed bile acids
      2. Steatorrhea and failure to thrive
      3. Low serum LDL cholesterol secondary to loss of cholesterol in bile acids
   E. Diagnosis
      1. Small intestine architecture is normal
      2. Diarrhea may improve with trial of cholestyramine (see Treatment for further details) and low-fat diet
      3. Bile acid absorption can be detected by measuring bile acid analogue 75 Se-homocholic acid-taurine test
   F. Treatment
      1. Cholestyramine binds bile acids and may prevent secretory diarrhea
      2. Cholestyramine does not prevent fat malabsorption and may even exacerbate it by binding bile acids, preventing micellar formation
      3. Low-fat diet with supplemental medium chain triglyceride (MCT). MCTs do not require bile acids for emulsification, as they can be directly absorbed into the portal system
      4. Fat-soluble vitamin deficiencies should be monitored and supplemented

IV. Congenital Chloride Diarrhea (see Diarrhea)
   A. Most common cause of congenital secretory diarrhea results from mutation in the SLC26A3 gene causing abnormality of Cl-/HCO3 exchange in the ileum and colon
   B. Diagnosis
      1. Fecal chloride concentration exceeds the sum of fecal sodium and potassium
      2. Metabolic alkalosis, hypochloremia, hypokalemia and hyponatremia
   C. Treatment
      1. Oral and/or parenteral KCl supplementation

V. Congenital Sodium Diarrhea
   A. Very rare impairment of intestinal sodium-hydrogen exchanger results in net sodium excretion by enterocyte
      1. There are 3 Na+-H+ transporters in the GI tract including NHE-2, NHE-3, NHE-4. NHE-2 and NHE-3 are expressed in the small intestine and NHE-4 is mainly in the gastric mucosa. A defect in NHE-3 is the possible primary cause of congenital sodium diarrhea
   B. Inheritance: autosomal recessive
   C. Clinical Manifestations
      1. Polyhydramnios due to in-utero diarrhea
      2. Dilated small bowel detectable on prenatal ultrasound suggest distal intestinal atresia
      3. Life-threatening diarrhea in the 1st week of life. Diarrhea is alkaline with high sodium concentration
      4. Hyponatremia and metabolic acidosis. Urine shows low-to-normal levels of sodium
      5. Association with choanal atresia has been noted
   D. Diagnosis
      1. Fecal stool sodium >90 mEq/L of stool water. Stool bicarbonate levels are also increased
      2. Hyponatremia and metabolic acidosis
      3. Normal or low urinary sodium
      4. Intestinal biopsies usually normal. Some show partial villous atrophy and decreased villus-to-crypt ratio
   E. Treatment
      1. Maintain fluid–electrolyte balance with oral and/or parental supplements
VI. Acrodermatitis Enteropathica
A. Primary acrodermatitis enteropathica: mutation of ZIP4 gene on chromosome 8q24.3 causes abnormal zinc transport through the apical membrane of gastric, intestinal, colonic and renal epithelium
   1. SLC39 proteins are members of the ZIP family of metal ion transporters that export into cell cytoplasm
   2. SLC39A4 has been implicated in the uptake of dietary zinc into intestinal enterocytes
B. Inheritance: autosomal recessive
C. Clinical Manifestations
   1. Presents earlier in patients who are exclusively breastfed, as breast milk is not an adequate source of zinc
   2. Anorexia, steatorrhea and failure to thrive
   3. Acral dermatitis on hands and feet. There is also a rash around the orifices, specifically, the mouth, anus, ears and nares (See Figure 2)
   4. Alopecia is seen in long-term zinc deficiency
   5. Other manifestations include poor wound healing and abnormalities of humoral and cell-mediated immune system. Neurologic manifestations include mental slowness and neurosensory problems
   6. Secondary zinc deficiency due to chronic diarrhea can present similar to primary acrodermatitis enteropathica
D. Diagnosis
   1. Low serum level of alkaline phosphatase, a zinc-dependent metalloenzyme
   2. Low serum and urinary zinc
   3. Small bowel histology: loss of villous architecture with increased cellular infiltration in the lamina propria. Enterocyte nuclei enlarged with chromatin
   4. Skin histology: nonspecific inflammation with intracellular edema and pallor of the upper third of the epidermis
E. Treatment
   1. Large doses of zinc supplementation

VII. Congenital Glucose-Galactose Malabsorption
A. Mutation in SGLT (sodium coupled glucose transporter) gene
   1. In homozygous state, inability to transport glucose and galactose in the intestinal and renal tubular epithelial cells
   2. SGLT couples the transport of two molecules of sodium with 1 molecule of glucose or galactose
B. Inheritance: autosomal recessive. Heterozygotes have mild clinically insignificant impairment of renal and intestinal glucose transport. Most common in Greenland Eskimos
C. Clinical Manifestations
   1. Life-threatening neonatal diarrhea, dehydration and metabolic acidosis. Diarrhea stops when feedings are withheld
D. Diagnosis
1. Diarrhea resolves on diet absent of glucose and galactose
2. Breath hydrogen test positive after glucose by mouth
3. Stool pH <5.3 due to bacterial fermentation of unabsorbed carbohydrate to acetate, butyrate and propionate
4. Stool osmolality increased
5. Stool Clinitest positive
6. Small intestine histology and disaccharidase activity are normal

E. Treatment
1. Carbohydrate-free formula with fructose as the carbohydrate source
2. Patients must be monitored carefully, as fructose absorption early in life may be limited
3. Older patients tolerate some dietary glucose. Generally, patients require a high-fat, high-protein diet throughout life

VIII. Fructose Malabsorption
A. Fructose malabsorption is a feature of 2 distinct clinical circumstances
1. Toddler’s diarrhea due to increase ingestion of fruit juices
2. GLUT 5 responsible for absorption of fructose across enterocyte brush border. In animals, GLUT 5 expression increases slowly during weaning
3. Perhaps relative deficiency is causative in human children drinking copious fruit juice
4. Isolated fructose malabsorption (IFM)—rare disorder resulting from mutations in the GLUT 5 gene causes lifelong fructose malabsorption

B. Inheritance: IFM is autosomal recessive
C. Clinical Manifestations
1. Toddler diarrhea: fruits and fruit juices produce abdominal cramping and osmotic diarrhea. Symptoms are dose-dependent
2. IFM: malabsorption of fructose is severe and not dose-dependent

D. Diagnosis
1. Usually clinical – improved symptoms with fructose-free diet
2. Fructose breath hydrogen test
3. Small intestinal histology is completely normal

E. Treatment
1. Fructose-free diet for toddler diarrhea can be titrated to tolerance. Need for strict fructose elimination improves with age
2. IFM patients: lifelong fructose elimination diet

IX. Hereditary Fructose Intolerance
A. Rare inborn error of metabolism often confused with fructose malabsorption
1. Disease results from deficiency of aldolase-B in liver, kidney and intestine
2. Aldolase B
   a. Critical in gluconeogenesis. Deficiency causes hypoglycemia
   b. Aldolase B mediates conversion of fructose-1-phosphate to dihydroxy-acetone-phosphage (DHAP) and glyceraldehyde. Enzyme deficiency blocks fructose metabolism at the formation of fructose-1-phosphate, preventing release of free phosphates needed in the metabolism of glycogen to glucose
   c. Fructose-1-phosphate accumulation and fructokinase inhibition allows free fructose in blood with eventual change in ATP-adenosine monophosphate (AMP) cellular ratio secondary to decreased free phosphate. The result is increased production of uric acid, with episodes of hyperuricemia and lactic acidosis. Hepatic and renal dysfunction is also seen

B. Inheritance: autosomal recessive
C. Clinical Manifestations
1. May be difficult to differentiate clinically from IFM. Most patients naturally avoid fructose-containing foods, including fruits
2. Patients with hereditary fructose intolerance are much sicker than patients with IFM after consumption of fructose with abdominal pain, nausea, hypoglycemia and weakness, which may progress to vomiting, irritability, lethargy, jaundice, seizures (from hypoglycemia) and liver failure
3. Patients may have scleral icterus and hepatomegaly ± splenomegaly during an acute episode
D. Diagnosis
1. Dietary history and symptoms give the best clue to diagnosis
2. Clinistest positive non–glucose-reducing sugar in the urine
3. Renal Fanconi syndrome with glucosuria, proteinuria and aminoaciduria. Serum electrolytes indicate renal tubular acidosis
4. Hepatic dysfunction
5. Dietary elimination of fructose causes improved symptoms
6. Liver biopsy may show focal necrosis, fatty degeneration in peripheral lobules, bile duct proliferation, and late changes of portal and biliary cirrhosis

E. Treatment
1. Eliminate fructose and sucrose from diet
2. Supportive care during acute episode
3. Avoiding triggers that cause acute episodes decreases risk of developing cirrhosis from repetitive insults

X. Lysinuric Protein Intolerance
A. Sole disorder of amino acid and peptide absorption causing GI symptoms
1. Mutation of SLC7A7 gene which encodes for the cationic amino acid transporter y+LAT-1 located on basolateral membrane of enterocyte, renal tubules and respiratory epithelium
   a. Responsible for transport of dibasic amino acids (lysine, arginine and ornithine) in exchange for Na⁺ and neutral amino acids
   b. Decreased absorption of arginine and ornithine results in urea cycle dysfunction and hyperammonemia

B. Inheritance: autosomal recessive

C. Clinical Manifestations
1. Failure to thrive, diarrhea and vomiting
2. Many patients have history of self-imposed restriction of protein intake
3. Chronic ingestion of protein enriched diet can result in irreversible mental retardation
4. Patients also present with marked hepatosplenomegaly and frequent bone fractures

D. Complications
1. Alveolar proteinosis is common possibly due to alterations in the immune system and accumulation of lipoprotein deposits in the alveoli
2. Osteoporosis due to decrease in essential amino acid lysine
3. Arginine deficiency may also be associated with vascular endothelial dysfunction, increasing risk of vascular abnormalities throughout life
4. Deficiency of total and antigen-specific immunoglobulin, resulting in increased risk of infections (T-cell function is normal)
5. Increased risk for hemophagocytic histiocytosis and systemic lupus

E. Diagnosis
1. Decreased plasma concentration of diamino acids
2. Urine organic acids show elevated lysine and orotic acid

F. Treatment
1. Systemic administration of the essential amino acid, lysine, has not improved clinical symptoms
2. Supplemental citrulline (200 mg/kg/d) and dietary protein restriction (not to exceed 1.5 g/kg/d). Citrulline is absorbed by neutral amino acid transporters and can subsequently replenish the urea cycle. Mealtime doses of citrulline are readily absorbed and decrease rates of postprandial hyperammonemia by providing needed substrate for the urea cycle
Recommended Reading


### 8K. Vitamin and Mineral Absorption, Function, and Deficiency States

Vitamins are essential organic compounds required in small amounts as cofactors in a wide range of metabolic functions of an organism. Deficiency typically results in specific symptoms and laboratory findings. Similarly, excessive levels may be toxic with characteristic presentations. Most vitamins and minerals can be assessed with laboratory testing.

<table>
<thead>
<tr>
<th>Fat-soluble Vitamins</th>
<th>Absorption</th>
<th>Function</th>
<th>Deficiency</th>
<th>Toxicity</th>
<th>Laboratory Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A (retinoid)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Location:</td>
<td>Upper small intestine</td>
<td>- Forms retinol for low light and color vision</td>
<td>Etiology:</td>
<td>- Fat malabsorption (pancreatic insufficiency, cholestatic liver disease, malabsorption)</td>
<td>- Alopecia</td>
</tr>
<tr>
<td>Dietary source:</td>
<td>Green leafy vegetables, carrots, sweet potatoes, liver, fish oil, kidney, dairy products and eggs</td>
<td>- Carbohydrate transfer to glycoprotein</td>
<td>- Dietary insufficiency</td>
<td>- Retinol</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Maintains epithelial integrity</td>
<td>Symptoms:</td>
<td>- Night blindness</td>
<td>- Retinol binding protein</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Required for cell proliferation</td>
<td></td>
<td>- Xerophthalmia</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Bitot spots</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>- Keratomalacia</td>
<td></td>
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<tr>
<td>Vitamin D (Ergocalciferol = D2, Cholecalciferol = D3)</td>
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<tr>
<td>Location:</td>
<td>Synthesis in skin (D3)</td>
<td>- Regulates calcium and phosphate levels through impact on absorption, but also renal excretion and bone mobilization</td>
<td>Etiology:</td>
<td>- Fat malabsorption</td>
<td>- Hypercalcemia (N/V, weakness, fatigue, diarrhea, anorexia, headache, confusion, psychosis and/or tremor)</td>
</tr>
<tr>
<td>Dietary source:</td>
<td>Absorbed from food in duodenum and distal small intestine</td>
<td>- Inadequate sun exposure</td>
<td>- Dietary insufficiency</td>
<td>- Hypercalcuria</td>
<td>- 25-OH Vitamin D</td>
</tr>
<tr>
<td></td>
<td>Fortified milk, liver, oils, sunlight, egg yolks</td>
<td>- Dietary insufficiency</td>
<td>- Symptoms:</td>
<td>- Rickets/osteomalacia</td>
<td>- Calcium</td>
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<td></td>
<td></td>
<td></td>
<td>- Dental caries</td>
<td>- Phosphorous</td>
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<td></td>
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<td>- Hypocalcemia/ hypophosphatemia</td>
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<td>- Increased alkaline phosphatase</td>
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<td></td>
<td></td>
<td></td>
<td>- Phosphaturia, aminoaciduria</td>
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</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Fat-soluble Vitamins</th>
<th>Absorption</th>
<th>Function</th>
<th>Deficiency</th>
<th>Toxicity</th>
<th>Laboratory Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E</td>
<td>Location:</td>
<td></td>
<td>Etiology:</td>
<td>Toxicity:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nonsaturable passive diffusion in jejunum</td>
<td>- Cell membrane antioxidant</td>
<td>- Fat malabsorption</td>
<td>- Impaired neutrophil function</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dietary source: Oil containing grains, plants and vegetables</td>
<td>- Free radical scavenger</td>
<td>- Inadequate intake (breastfed infants)</td>
<td>- Coagulopathy</td>
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<td></td>
<td></td>
<td>- Inhibits polyunsaturated fatty acid oxidation</td>
<td>- Chronic antibiotic therapy</td>
<td>- Thrombocytopenia</td>
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<td></td>
<td></td>
<td></td>
<td>Symptoms:</td>
<td>- Cerebral hemorrhages</td>
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<td></td>
<td></td>
<td></td>
<td>- Anemia/hemolysis</td>
<td></td>
<td>Plasma Alpha-tocopherol</td>
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<td></td>
<td></td>
<td></td>
<td>- Neurologic deficit (ocular palsy, wide-based gait, decreased DTR's)</td>
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<td></td>
<td></td>
<td></td>
<td>- Altered prostaglandin synthesis</td>
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<tr>
<td>Vitamin K</td>
<td>Location:</td>
<td></td>
<td>Etiology:</td>
<td>Toxicity:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Saturable, energy dependent absorption in jejunum</td>
<td>- Carboxylation and activation of clotting factors</td>
<td>- Fat malabsorption</td>
<td>- Not well understood</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dietary source: Leafy vegetables, soybean oil, fruits, seeds, cow milk, liver</td>
<td>- Affects bone formation</td>
<td>- Inadequate intake (breastfed infants)</td>
<td>- PT</td>
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<td></td>
<td></td>
<td></td>
<td>Symptoms:</td>
<td>- Abnormal bone matrix synthesis</td>
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<td></td>
<td></td>
<td></td>
<td>- Coagulation/ prolonged PT</td>
<td>- Inadequate levels of vitamin K dependent clotting factors (II, VI, IX, X)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>- Abnormal bone matrix synthesis</td>
<td>- Plasma phylloquinone</td>
<td></td>
</tr>
<tr>
<td>Water-soluble Vitamins</td>
<td>Absorption</td>
<td>Function</td>
<td>Deficiency</td>
<td>Toxicity</td>
<td>Laboratory Measurement</td>
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<tr>
<td><strong>Vitamin C</strong> (Ascorbic acid and dehydroascorbic acid)</td>
<td><strong>Location:</strong> - Predominantly ileum via saturable, sodium - energy dependent active transport</td>
<td><strong>Dietary source:</strong> Citrus fruits, papaya, tomatoes, cabbage, potatoes, cantaloupe, strawberries</td>
<td><strong>Absorption Function Deficiency</strong></td>
<td><strong>Toxicity</strong></td>
<td><strong>Laboratory Measurement</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Antioxidant:</strong> reacts directly with superoxide, hydroxyl radicals and singlet oxygen</td>
<td><strong>Deficiency:</strong> - Inadequate intake - Cigarette smoking</td>
<td><strong>Symptoms:</strong> MILD DEFICIENCY: - Anorexia - Fatigue - Muscle pain</td>
<td><strong>Deficiency:</strong> SEVERE DEFICIENCY: - Scurvy: anemia, bleeding gums, petechiae, perifollicular hemorrhage, impaired wound healing, joint effusions, fatigue, depression, and/or weakening of collagen in bone, teeth, and connective tissue, sudden death</td>
<td>- Very high doses cause gastric irritation and renal dysfunction - Supplementation should be avoided in renal failure, kidney stones, iron overload disease, and/or individuals receiving heparin or warfarin</td>
</tr>
<tr>
<td><strong>Vitamin B</strong></td>
<td><strong>Location:</strong> See following page</td>
<td><strong>Dietary source:</strong> Oats, swiss chard, eggs, soy</td>
<td><strong>Absorption Function Deficiency</strong></td>
<td><strong>Toxicity</strong></td>
<td><strong>Laboratory Measurement</strong></td>
</tr>
<tr>
<td><strong>Biotin</strong></td>
<td><strong>Location:</strong> - Absorbed in jejunum</td>
<td><strong>Dietary source:</strong> Oats, swiss chard, eggs, soy</td>
<td><strong>Absorption Function Deficiency</strong></td>
<td><strong>Toxicity</strong></td>
<td><strong>Laboratory Measurement</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Coenzyme for carboxylases, and transcarboxylases</strong></td>
<td><strong>Etiology:</strong> - Raw egg consumption - Prolonged antibiotic therapy - TPN - Anticonvulsant therapy</td>
<td><strong>Symptoms:</strong> - Multiple carboxylase deficiency - Organic acidemia/acidosis - Dermatitis/aloepecia - CNS: seizures/ataxia/depression</td>
<td><strong>No toxicity</strong></td>
<td>- Serum biotin or 24-hour urine collection (most valid) – decreased urinary excretion of biotin and increased excretion of 3-hydroxyisovaleric acid</td>
</tr>
</tbody>
</table>
B Vitamins

- **Vitamin B<sub>1</sub> (Thiamine)**
  - Coenzyme in metabolism of carbohydrates and branched AAs
  - Absorption in the proximal jejunum by carrier mediated mechanisms at low concentrations and passive diffusion at high concentrations
  - Deficiency results in calf tenderness, hyporeflexia, severe lethargy, irritability, restlessness along with wet and/or dry Beriberi
    - Wet Beriberi – primarily cardiac involvement (dilated cardiomyopathy, edema, cardiac failure)
    - Dry Beriberi – primarily damage to nerves (Wernicke encephalopathy, Korsakoff psychosis, paresthesias, weakness, ophthalmoplegia, nystagmus)
    - Infantile Beriberi – occurs in undeveloped countries related to breastfeeding mother with inadequate intake of thiamine (primarily due to polished rice-based diet), usually between 2–3 months of age. Chronic form characterized by lethargy, anorexia, vomiting, constipation or diarrhea, with hypotonia. In the acute form, cardiac enlargement, generalized edema and tachycardia rapidly develops after these initial symptoms, followed by aphonia, severe weakness, loss of reflexes, coma and death
  - Laboratory measurement utilizes erythrocyte transketolase activity with and without in vivo addition of thiamine pyrophosphate

- **Vitamin B<sub>2</sub> (Riboflavin)**
  - Involved in metabolism of carbohydrates, fats, ketone bodies and AAs
  - Absorption in the proximal small intestine via Na-dependent carriers
  - Deficiency results in angular stomatitis, cheilosis, glossitis, seborrheic dermatitis, normocytic anemia, reduced growth in children
  - Infants on prolonged phototherapy may be at risk for deficiency
  - Laboratory measurement utilizes erythrocyte glutathione reductase activity. 24-hour urinary riboflavin <30 mcg/day

- **Vitamin B<sub>3</sub> (Niacin)**
  - Precursor of NAD+/NADH and NADP+/NADPH which are involved in cellular metabolism, DNA repair and the production of steroid hormones
  - Absorption in stomach and intestine by active transport and passive transport at high concentrations
  - Deficiency occurs where corn is a staple food and results in pellagra – classic signs are the 4 D’s (dermatitis, diarrhea, dementia, death)
    - Hartnup disease is a hereditary nutritional disorder caused by abnormal tryptophan (a precursor of niacin) absorption and metabolism. Infants present with failure to thrive, photosensitivity, ataxia, nystagmus and tremor. Symptoms may not begin until early adulthood with a pellagra-like dermatosis on sun-exposed skin. Treatment includes a high-protein diet, sun avoidance and niacin supplementation
  - Toxicity – vasodilation, itching, sensitization to heat, headache, GI irritation, hepatitis, glucose intolerance and myopathy
  - Laboratory measurement of urine excretion of niacin-methylated metabolites

- **Vitamin B<sub>5</sub> (Pantothenic Acid)**
  - Required for the synthesis of coenzyme A (CoA), which is important for energy metabolism and acetylation of alcohol and amines
  - Absorption is by both passive diffusion and by Na-dependent active transport
  - Deficiency results in postural hypotension, anorexia and vomiting, and hyperreflexia
  - Toxicity is very rare
  - Laboratory measurement is by levels in whole blood or 24-hour urine collection
• Vitamin B₆ (Pyridoxine)
  o Required for Hgb synthesis, maintenance of sodium/potassium balance, immune and nervous function, and maintenance of glucose homeostasis
  o Absorption by passive diffusion in the jejunum
  o Deficiency results in dermatitis, glossitis, depression, confusion, seizures and anemia. Deficiency is most commonly associated with use of isoniazid
  o Toxicity occurs with excessive vitamin supplementation and results in reversible ataxia and severe sensory neuropathy
  o Laboratory measurement utilized plasma pyridoxal phosphate and 24-hour urine excretion

• Vitamin B₉ (Folate/Folic Acid)
  o Involved in synthesis, repair and function of DNA, helps in RBC production, helps with neural tube formation
  o Absorption by passive diffusion in the jejunum
  o Deficiency results in increased risk of low birth weight and prematurity, increased risk of neural tube defects, anemia, delayed growth, diarrhea, headaches, weakness
  o Patients with alcohol abuse or with chronic use of anticonvulsants are at risk for deficiency
  o Methotrexate interferes with the biosynthesis of folic acid, so patients on this medication should be supplemented
  o Laboratory measurement of plasma folate levels

• Vitamin B₁₂ (cyanocobalamin)
  o Catalyzes reactions required for formation of methyl donor DNA and RNA, and reactions required for Hgb synthesis and fat/protein metabolism
  o Absorption in ileum is dependent on intrinsic factor
  o Deficiency results in megaloblastic anemia and neurological symptoms, such as weakness, paresthesias and confusion
  o Pernicious anemia
    • Autoimmune disorder resulting in destruction of parietal cells, achlorhydia, and failure to produce intrinsic factor
  o Vitamin B₁₂/Folate Deficiency
    • Treat with Vitamin B₁₂ first! This will address both anemia and neurological symptoms
  o Who is at risk for deficiency?
    • Celiac disease, Crohn disease, post-bariatric surgery, post-ileal resection, vegetarians/vegans
  o Laboratory measurement by serum B₁₂ levels
<table>
<thead>
<tr>
<th>Mineral and Trace Elements</th>
<th>Absorption</th>
<th>Function</th>
<th>Deficiency</th>
<th>Toxicity</th>
<th>Laboratory Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Calcium</strong></td>
<td>Location:</td>
<td>- Bone structure - Important metabolic regulator - Maintains nerve excitation threshold</td>
<td>Etiology: - Inadequate intake - Vitamin D deficiency</td>
<td>Symptoms: - Bone demineralization - Tetany/seizures - Cardiac arrhythmias</td>
<td>- Early: Fatigue, nausea, vomiting, constipation, anorexia, and confusion - Late: Cardiac arrhythmia, bradycardia</td>
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<td></td>
<td>Duodenum</td>
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<td></td>
<td>Mobilization from bone stores when serum levels low</td>
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<tr>
<td></td>
<td>Dietary source: Milk, yogurt, cheese</td>
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<tr>
<td><strong>Chromium</strong></td>
<td>Location:</td>
<td>- Glucose tolerance factor - Metabolism of nucleic acids - Trivalent Cr potentially toxic: rhabdomyolysis, liver dysfunction, renal failure</td>
<td>Etiology: - Pregnancy and lactation</td>
<td>Symptoms: - Glucose intolerance - Neuropathy/encephalopathy - Altered nitrogen metabolism - Increased serum fatty acids</td>
<td>- No accurate tests due to very low levels in body - Can use serum, erythrocyte, and urine values if necessary</td>
</tr>
<tr>
<td></td>
<td>Soluble in stomach, absorbed via nonmediated passive diffusion in jejunum</td>
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<tr>
<td></td>
<td>Dietary source: Whole grains, cheese, lean meats, fruits and vegetables</td>
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<tr>
<td><strong>Copper</strong></td>
<td>Location:</td>
<td>- Essential component of several oxidative enzymes (superoxide dismutase, cytochrome oxidase, catalase) - Involved in energy production, bone strength, Hgb synthesis, protection of cell membranes from oxidative damage, and neurological development</td>
<td>Etiology: - Inadequate intake</td>
<td>Symptoms: - Nausea - Vomiting - Liver and kidney damage</td>
<td>- Serum copper, ceruloplasmin - Liver biopsy - Estimate abnormal storage of Cu - Superoxide dismutase activity</td>
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<td></td>
<td>Stomach and small intestines - Transported to the liver bound to albumin and incorporated into ceruloplasmin</td>
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<tr>
<td></td>
<td>Dietary source: Liver, veal, shell fish</td>
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<tr>
<td><strong>Iodide</strong></td>
<td>Location:</td>
<td>- Component of thyroid hormones</td>
<td>Etiology: - Inadequate intake</td>
<td>Symptoms: - Goiter - Neurologic abnormalities - Anemia - Osteoporosis - Brittle hair</td>
<td>- Rare</td>
</tr>
<tr>
<td></td>
<td>Stomach and upper SI</td>
<td></td>
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<tr>
<td></td>
<td>Dietary source: Sea vegetables, milk, eggs, fish</td>
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<thead>
<tr>
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<th>Function</th>
<th>Deficiency</th>
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<th>Laboratory Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron</td>
<td>Location:</td>
<td>- Heme synthesis</td>
<td>- Inadequate intake</td>
<td>- Wide range from acute poisoning with overdose to chronic iron overload and subsequent organ damage</td>
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<tr>
<td></td>
<td>- Duodenum and jejunum</td>
<td>- Component of cytochromes</td>
<td>- Parasitic worms</td>
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<td></td>
<td>- Ferrous iron is most easily absorbed</td>
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<td>- Chronic blood loss</td>
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<td></td>
<td>- Vitamin C, HCl, lactic acid, and amino acids, aspartic and glutamic acid promote ferrous form</td>
<td></td>
<td>- PICA</td>
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<tr>
<td>Dietary source:</td>
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<td></td>
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<tr>
<td>Meat, fish and poultry</td>
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<tr>
<td>Magnesium</td>
<td>Location:</td>
<td>- Cofactor of hexokinase and phosphokinase</td>
<td>- Inadequate intake</td>
<td>- Nausea, vomiting, diaphoresis, flushing, depressed mental function- ing, drowsiness, muscular weakness, hypotension, bradycardia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Distal jejunum and ileum</td>
<td>- Alters ribosomal aggregation in protein synthesis</td>
<td>- Malabsorption</td>
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<td></td>
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<td>- Increases nerve excitation threshold</td>
<td>- Diuretic use</td>
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<td></td>
<td></td>
<td></td>
<td>- Pregnancy</td>
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<td>Dietary source:</td>
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<td>Whole greens, nuts and green leafy vegetables</td>
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<tr>
<td>Manganese</td>
<td>Location:</td>
<td>- Enzyme activator</td>
<td>- Very rare in those with enteral nutrition</td>
<td>- Whole blood levels</td>
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<td></td>
<td>- Throughout SI with quickly saturable state</td>
<td>- Mucopolysaccharide synthesis</td>
<td>- CNS abnormalities: hyperirritability, violent acts, hallucinations and ataxia</td>
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<td>- Cholesterol synthesis</td>
<td>- Deposition in basal ganglia produces Parkinson-like syndrome</td>
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<td></td>
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<td>- Cartilage/bone formation</td>
<td>- Immune dysfunction</td>
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<td></td>
<td></td>
<td>- Pyruvate carboxylase cofactor</td>
<td>- Nephritis, pancreatitis, hepatitis, orchitis</td>
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<td></td>
<td></td>
<td>- Superoxide dismutase cofactor</td>
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<td></td>
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<tr>
<td>Dietary source:</td>
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<tr>
<td>Green leafy vegetables and maple syrup</td>
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<th>Toxicity</th>
<th>Laboratory Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphorus</td>
<td>Location: Small intestine</td>
<td>Bone structure, Cell membrane structure, Energy storage, Acid-base balance: buffering, Oxygen release (2,3-DPG)</td>
<td>Etiology: - Inadequate intake, - TPN, - Hypoparathyroidism, - Renal losses, - Refeeding syndrome</td>
<td>Symptoms: - Tissue hypoxia, - Respiratory failure (ventilatory dependence), - Rickets, - CNS abnormalities</td>
<td>- Diarrhea, - Calcification of organs and soft tissue, - Serum phosphorous levels</td>
</tr>
<tr>
<td>Selenium</td>
<td>Location: Small intestine</td>
<td>- Prevent cellular damage from free radicals, - Regulates thyroid function, - Role in immune function</td>
<td>Etiology: Inadequate intake</td>
<td>Symptoms: - Poor cardiac function, - Osteoarthropathy, - Hypothyroidism</td>
<td>- Hair loss, - Muscle cramps, - Diarrhea, - Nausea, - Vomiting, - Serum selenium, - Nail and hair selenium, - Glutathione peroxidase activity</td>
</tr>
<tr>
<td>Zinc</td>
<td>Location: Small intestine</td>
<td>- Catalytic activity of over 100 enzymes, - Immune function, - Protein synthesis, - Wound healing, - DNA synthesis and cell division</td>
<td>Etiology: Inadequate intake</td>
<td>Symptoms: - Delayed growth, hypogonadism, - Hair loss, skin lesions, - Impaired immune function, - Diarrhea</td>
<td>- Nausea, - Vomiting, - Decreased immune function, - Altered copper and iron function, - Reduced HDL, - Serum zinc, - Alkaline phosphatase, - RBC zinc concentrations</td>
</tr>
</tbody>
</table>

**Recommended Reading**

ASPEN. *Nutrition Support Core Curriculum: A Case-Based Approach - The Adult Patient.*


I. **Indispensable amino acids**
20 amino acids that cannot be synthesized by humans in sufficient amounts for needs (also called dietary essentials)
   A. Conditionally indispensable amino acids are normally synthesized in sufficient amounts, but during rapid growth or unusual metabolic needs, amount synthesized becomes insufficient for needs
      1. Table 1 shows the amino acids required for protein synthesis, indicating which are indispensable and which are conditionally indispensable
      2. Protein constitutes ~20% of adult body weight, 2% of infant body weight, <2% in preterm infants

II. **Protein turnover**
   A. Protein turnover is a continuous process of endogenous protein breakdown and synthesis
      1. Amount of daily protein turnover far exceeds daily amino acid intake
   B. Protein turnover provides constant flux of amino acids through all body compartments
   C. Measurable free plasma amino acid represents a small percentage of the whole body amino acid content
   D. Table 2 shows the body organ systems of importance in essential amino acid metabolism

III. **Amino acid toxicity**
   A. Occurs with genetic defects of amino acid metabolism
   B. Occurs with damage or bypass of major organ systems involved in amino acid metabolism
      1. Parenteral nutrition bypasses the regulatory influence of the intestine
      2. Intestinal bypass for obesity prevents absorption
   C. Table 3 shows common indispensable amino acids that can be toxic in excess and the typical signs and symptoms

IV. **Amino acid deficiency**
   A. Amino acid deficiency is a much more important global nutritional problem than amino acid toxicity
   B. Growth restriction is the most important sign of an amino acid deficiency in childhood
   C. Additional signs of amino acid deficiency:
      1. anorexia
      2. decreased plasma concentration of the most limiting amino acid

V. **Principle of amino acid metabolism**
   A. Rate of protein synthesis and rate of growth are determined by the first limiting amino acid
   B. Protein synthesis is optimal when all amino acids are present at or above their requirement
   C. Deficiency of a single amino acid may cause suboptimal protein synthesis and restricted growth, even when other amino acids are available in excess
   D. Normal amino acid metabolism requires vitamin cofactors. Cofactor deficiency may mimic certain amino acid deficiencies
      1. Vitamin B_6_ – histidine, methionine, phenylalanine, tryptophan, branch chain amino acids
      2. Folates and vitamin B_12_ – methionine, phenylalanine
      3. Nicotinic acid/B3 – tryptophan
      4. Biotin/B7 – lysine
VI. Specific amino acid deficiency syndromes

A. Phenylalanine deficiency syndrome in infants receiving therapy for PKU presents with failure to thrive, neurological signs and eczema.

B. Isoleucine deficiency in infants receiving branch chain amino acid-free formula for MSUD may cause failure to thrive and acrodermatitis enteropathica.

Table 1. indispensable, Dispensable and Conditionally Dispensable Amino Acids in the Human Diet

<table>
<thead>
<tr>
<th>Indispensable</th>
<th>Dispensable</th>
<th>Conditionally Dispensable</th>
<th>Scenario</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histidine^a</td>
<td>Alanine</td>
<td>Arginine</td>
<td>Intestinal bypass – as crucial site for synthesis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Trauma and critical illness – increased demand beyond synthesis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Prematurity (hyperammonia observed with arginine free TPN)</td>
</tr>
<tr>
<td>Isoleucine^b</td>
<td>Aspartate</td>
<td>Cysteine^d</td>
<td>Liver disease – site of transulfuration from methionine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Prematurity – low cystathionase activity</td>
</tr>
<tr>
<td>Leucine^b</td>
<td>Asparagine</td>
<td>Glutamine</td>
<td>Trauma and critical illness – increased demand and also shunting away from muscle to visceral compartments</td>
</tr>
<tr>
<td>Lysine</td>
<td>Glutamate</td>
<td>Glycine</td>
<td>Prematurity – increased demand during rapid growth</td>
</tr>
<tr>
<td>Methionine^c</td>
<td>Serine</td>
<td>Proline</td>
<td>Intestinal bypass – as crucial site for synthesis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Critical illness – increased demand beyond synthesis</td>
</tr>
<tr>
<td>Phenylalanine^d</td>
<td></td>
<td>Tyrosine</td>
<td>Prematurity – low phenylalanine hydroxylase activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Renal disease – uremia inhibits phenylalanine hydroxylase activity</td>
</tr>
</tbody>
</table>

^aDeficiency states with growth failure have not been described, but chronic deficiency in adults has shown a fall in plasma level, with improved nitrogen balance if supplemented.

^bKnown as the branched chain amino acids.

^cKnown as the sulfur amino acids.

^dKnown as the aromatic amino acids.

Table 2. Organ Sites Important in Indispensable Amino Acid Metabolism

<table>
<thead>
<tr>
<th>Indispensable Amino Acid</th>
<th>Major Organ Sites of Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histidine</td>
<td>skin, intestine, liver, kidney</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>muscle, kidney</td>
</tr>
<tr>
<td>Leucine</td>
<td>muscle, kidney</td>
</tr>
<tr>
<td>Lysine</td>
<td>liver, intestine</td>
</tr>
<tr>
<td>Methionine</td>
<td>intestine, liver, muscle</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>liver, central nervous system, kidney</td>
</tr>
<tr>
<td>Threonine</td>
<td>intestine^a, liver</td>
</tr>
<tr>
<td>Tryptophan^d</td>
<td>central nervous system, liver</td>
</tr>
<tr>
<td>Valine^b</td>
<td>muscle, kidney</td>
</tr>
</tbody>
</table>

^aMucin formation
### Table 3. Toxic Indispensable Amino Acids in Excess

<table>
<thead>
<tr>
<th>Indispensable Amino Acid</th>
<th>Potential Causes of Toxicity/Excess</th>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methionine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Implicated in parenteral nutrition associated liver disease; high plasma level in chronic liver disease with malnutrition</td>
<td>Potential to cause liver disease and elevate plasma homocysteine levels, with risk of thrombosis or atherogenesis</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>Phenylketonuria – inborn error of phenylalanine hydroxylase</td>
<td>Neonatal death, mental retardation, growth impairment</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>Food supplements</td>
<td>Serotonergic, nausea, drowsiness, appetite suppression, MAOI interaction</td>
</tr>
<tr>
<td>Leucine, isoleucine and valine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Maple Syrup Urine Disease – inborn error of branch chain ketoacid dehydrogenase</td>
<td>Neonatal death, mental retardation, high plasma and urine leucine level</td>
</tr>
</tbody>
</table>

<sup>a</sup>Theoretical or animal data.  
<sup>b</sup>Theoretically could compete for membrane transport of tryptophan and tyrosine with potential for neurotoxicity (observed in animals).

### Recommended Reading

Furst P, Stehle P. What are the essential elements needed for determination of amino acid requirements in humans? *J Nutr.* 2004;143:1558S-1565S.


Reeds PJ. Dispensable and indispensable amino acids for humans. *J Nutr.* 2000;130: 1835S-1840S.
Several medical conditions require modification of nutritional intake as an integral part of therapy. Some common conditions requiring nutrition therapy include refractory seizures, cystic fibrosis, cholestasis, diarrhea, celiac disease, disaccharidase deficiency, food allergy, malnutrition and obesity. Each condition has specific indications for initiation of nutrition therapy. It is important to monitor children for complications associated with a restricted diet.

I. Ketogenic Diet
   A. Overview and Pathophysiology
      1. Ketogenic diet consists of 3 or 4 parts (by weight) fat to one part protein and/or carbohydrate
      2. High fat and low carbohydrate diet produces persistent ketosis
      3. Ketosis has a direct antiseizure effect
   B. Indications
      1. Refractory partial or generalized seizures
      2. Symptomatic generalized epilepsy syndromes i.e., infantile spasms, Lennox-Gastaut, GLUT-I deficiency, pyruvate dehydrogenase deficiency, myoclonic-astatic epilepsy, tuberous sclerosis, Rett syndrome
      3. Intractable focal epilepsy
      4. Contraindications:
         a. Absolute—defects in fatty acid oxidation, porphyria, pyruvate carboxylase deficiency
         b. Relative—certain mitochondrial cytopathies, carnitine deficiencies, other disorders of fat metabolism
   C. Implementation and Monitoring
      1. Usually done in the inpatient setting
      2. Patients fast except for sugar-free fluids for 24 hours, blood glucose is checked q6h
      3. Feeding is then gradually started and increased to full caloric intake over 2–3 days
      4. Modification of the diet from 4:1 to 3:1 lipid:nonlipid ratio improves tolerability for older children but may lessen ketosis and allow recurrence seizures
      5. The level of ketosis is monitored in urine or serum
      6. The nutritional content of all meals must be calculated and each item weighed and measured
      7. Ketocal® and Ross carbohydrate-free are commercially available formulas which can be used
      8. Supplementation with a multivitamin, minerals and carnitine is recommended
      9. Clinical response occurs within a few weeks to 2 months
      10. The diet should be gradually discontinued after 2 years
   D. Complications
      1. Dehydration usually during initial fasting phase
      2. GI complaints: diarrhea, gastroesophageal reflux, nausea, vomiting, constipation
      3. Pancreatitis
      4. Cardiomyopathy due to selenium deficiency
      5. Metabolic complications: acidosis, hyperuricemia, hypoproteinemia, hypomagnesemia and hyponatremia
      6. Renal stones
      7. Osteopenia and decreased height velocity
II. Cystic Fibrosis

A. Overview
1. Better nutritional status in patients with CF is associated with improved FEV1 and improved survival
2. Malnutrition results from discrepancy between energy and micronutrient requirements and food intake modified by malabsorption
3. Higher energy intake results in better weight gain
4. Energy needs in CF are 110%–200% of energy needs for the healthy population of similar age, sex and size

B. Pathophysiology
1. Loss of CFTR function limits fluid secretion in the pancreas, resulting in a more viscous and acidic fluid in the pancreatic ducts
2. Lower pH prematurely activates trypsin and other zymogens, which cannot be flushed from the pancreas
3. Results in recurrent injury, progressive fibrosis and chronic pancreatitis
4. Insufficient production and secretion of pancreatic enzymes causes malabsorption of fat, protein and micronutrients, especially fat-soluble vitamins A, D, E and K
5. 85%–90% of patients have pancreatic insufficiency
6. Other gastrointestinal abnormalities may contribute to malnutrition: CF-related liver disease, bile salt abnormalities, CF-related diabetes mellitus, altered motility, small bowel bacterial overgrowth, gastroesophageal reflux disease, distal intestinal obstruction syndrome and constipation
7. Progressive lung disease and increased work of breathing increases caloric requirements. Chronic and recurrent infections, may reduce appetite and cause cytokine-induced catabolic state

C. Recommendations
1. BMI percentile is a more sensitive predictor of pulmonary outcomes than % of ideal body weight for age or for height
2. Children diagnosed before age 2 years should reach a weight for length >50th percentile by age 2 years
3. For older children and adults, the goal is BMI ≥50th percentile for age
4. For growth deficits, the first line is intensive treatment with behavioral intervention, nutritional counseling and use of oral nutritional supplements
5. When oral nutrition fails, enteral tube feeding should be used
6. Pancreatic enzyme replacement therapy should be given just prior to each meal, with half the dose given for snacks (see section on Pancreatic Enzymes)
7. Blood tests to evaluate nutritional status should be done at least annually: vitamin A, D and E levels, calcium, phosphorus, PTH, dexa scan, CBC, serum sodium, albumin and blood glucose

D. Dietary Supplementation
1. Vitamin supplementation in international units/day

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Infants &lt; 1 year</th>
<th>1–3 years</th>
<th>4–8 years</th>
<th>&gt;8 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1,500</td>
<td>5,000</td>
<td>5,000–10,000</td>
<td>10,000</td>
</tr>
<tr>
<td>D</td>
<td>400</td>
<td>800</td>
<td>800</td>
<td>800</td>
</tr>
<tr>
<td>E</td>
<td>40–50</td>
<td>80–150</td>
<td>100–200</td>
<td>200–400</td>
</tr>
<tr>
<td>K</td>
<td>0.3–0.5 mg/day</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. Because of sodium losses in sweat, patients with CF are prone to hyponatremic dehydration in heat stress and may need sodium chloride supplementation
III. Cholestasis (see section on Nutritional Consequences of Cholestasis)

A. Overview
1. Causes of cholestasis: biliary atresia, intestinal failure–associated liver disease (IFALD), Alagille syndrome, alpha-1-antitrypsin deficiency, progressive familial intrahepatic cholestasis, metabolic conditions
2. Nutritional goals for children with cholestasis: meet caloric needs, correct nutritional deficiencies, and minimize hepatotoxicity

B. Causes of Malnutrition in Pediatric Chronic Liver Disease
1. Abdominal distension and early satiety
2. GERD and caloric loss
3. Poor palatability of semielemental diet
4. Restriction of protein, water and calories
5. Fat malabsorption
6. Poor duodenal alkalinization leading to zinc and calcium malabsorption
7. Portal hypertension and bleeding
8. Ascites and protein loss
9. Liver dysfunction and impaired protein synthesis

C. Dietary Recommendations
(see section on Nutritional Consequences of Cholestasis)

D. Strategies for prevention of intestinal failure-associated liver disease (see intestinal failure)
1. Maximize enteral tolerance and stimulation, with both oral and tube feedings
2. Consider use of fish oil–based fat emulsions
3. Limit the total amount of lipid infusion
4. Alternate high and low protein formulations to prevent toxicity due to concentrated amino acids
5. Ursodeoxycholic acid protects against hepatotoxicity from toxic bile acids, stimulates bile flow, increases levels of glutathione (an antioxidant) and inhibits hepatocyte apoptosis

IV. Diarrhea — Acute

A. Overview
1. Defined as diarrhea with duration <3 weeks
2. Usually self-limiting, most often infectious

B. Dietary Recommendations
1. First step is repletion of fluid deficit and ongoing fluid losses
2. Once rehydration is complete, resume a balanced diet per ADA guidelines for age
3. Breastfeeding during oral rehydration appears to reduce the number, volume and duration of diarrheal stools
4. Full-strength cow’s milk and other nonhuman milks usually can be tolerated without problems. Dilution and substitution of lactose-free formulas usually is unnecessary
5. Foods containing high levels of fats and simple sugars are less well tolerated than are those with complex carbohydrates, lean meats, yogurt, fruits and vegetables
6. Use of the BRAT diet (banana, rice, applesauce, toast) or clear liquid diets (pediatyte and juices) should not be used for more than 24 hours. They provide suboptimum nutrition and there is little proof of efficacy in acute diarrhea

V. Diarrhea — Chronic

A. Overview
1. Defined as: diarrhea with duration of 4 weeks or more
2. Differential diagnosis:
   a. Bacterial, viral or parasitic agents
   b. Carbohydrate intolerance
   c. Milk or soy allergy
   d. Anatomic abnormalities, inflammatory bowel disease, celiac, cystic fibrosis
   e. Rare congenital disorders
   f. Immunodeficiency states
B. Interventions Based on Suspected Causes

1. Chronic nonspecific diarrhea of childhood: reassurance, high fiber, high fat, avoid intake of fluids containing fructose and sorbitol
2. Inflammatory bowel disease: exclusive enteral nutrition using hypoallergenic liquid diet may suppress intestinal inflammation and promote mucosal healing. Enteral nutrition can also be used as a supplement to increase caloric intake and promote growth. Patients should be monitored for micronutrient deficiencies with replacement as needed
3. Short bowel syndrome: young children may require a protein hydrolysate or elemental formula. Fiber supplementation enhances adaption via increased short chain fatty acid production and retention of stool water. Medium-chain triglycerides are used in patients with cholestasis
4. Celiac disease: gluten-free diet
5. Allergic enteropathy—elimination of some or all of the following highly allergenic foods: milk, eggs, fish, crustacean shellfish, tree nuts, peanuts, wheat and soybeans
6. Autoimmune enteropathy/IPEX: hydrolyzed, hypoallergenic formula to reduce antigen exposure
7. Congenital chloride diarrhea: high chloride intake to prevent volume depletion
8. Glucose-galactose malabsorption: fructose-based formula, lifelong dietary restriction of glucose and galactose
9. Congenital sucrase-isomaltase deficiency: elimination of sucrose, use of yeast based sucrase (sacrosidase) enzyme replacement therapy

Recommended Reading


I. Nutritional Supplementation

A. Indications for Enteral Nutrition/Parenteral Nutrition

1. Preexisting nutritional deprivation
2. Anticipated or current inadequate energy intake by mouth
   a. Unable to take PO 3–7 days or sooner in the presence of weight loss or catabolic stress and in preterm/LBW infants
3. Significant multiorgan system disease
   a. GI, renal, hepatic, cardiac, hematologic, pulmonary, burns

B. Enteral nutrition by mouth or tube is always preferable to IV nutrition if possible. Contraindications include:

1. Ileus
2. Bowel ischemia
3. Persistent or bilious emesis
4. Intestinal obstruction

C. Parenteral Nutrition (PN)

1. Indications
   a. Premature, LBW Infants
   b. Intestinal Failure
      1) Congenital and acquired lesions of the GI tract (short bowel syndrome)
         a) NEC, intestinal atresia, gastroschisis
      2) Intractable GI dysmotility/malabsorption
         a) Chronic intestinal pseudoobstruction, microvillus inclusion disease, tufting enteropathy, total aganglionic Hirschsprung disease

2. Definition
   a. Nutrition given intravenously, bypassing the usual process of eating and digestion
   b. Provides macronutrients (carbohydrates, protein, fat) and micronutrients (minerals, vitamins, trace elements)

3. Intravenous access may be central or peripheral
   a. Peripheral: IV or PICC
      1) Appropriate for patient with normal nutritional status without fluid restriction, likely to tolerate enteral nutrition (EN) in <2 weeks
      2) Limited nutrient concentration due to osmolarity restriction (300–900 mOsm/L)
         a) Osm= (Dex x 50) + (%AA x 100) + 2 (Na + K + Ca + Mg mEq/L)
         b) usual concentration of dextrose is 10-12.5 g/dL and usual concentration of protein is 2 g/dL
   b. Central catheter: PICC, Broviac, Hickman, Port
      1) Placed in large central vein to reduce damage to veins from the catheter and infusate (thrombophlebitis)
         a) High blood flow in central veins rapidly dilutes concentrated solutions
      2) Appropriate for patient with intolerance for more than 2 weeks regardless of initial nutritional status
4. Complications of PN
   a. Infection of line
      1) Interrupt PN infusion as little as possible
      2) *Staph epidermidis, Staph aureas, Candida* are the most common infecting organisms
   b. Technical complications of line placement
      1) Extravasation of fluid into pericardial or pleural space
         a) Usually presents with severe hemodynamic instability
      2) Pneumothorax
      3) Brachial plexus injury
      4) Air Emboli
      5) Venous thrombosis and thrombophlebitis
      6) Subcutaneous infiltration of PN solution causing with infection, pain and slough
   c. Bone disease (Insufficient Ca, Phos)
   d. PN-Associated Liver Disease (see below)

5. Components of PN
   a. Carbohydrate
      1) Given as glucose (D5-25%)
      2) Provides majority of total (55%) and non-protein calories (60%) for energy expenditure
      3) Primary energy source for brain
      4) Caloric density: 3.4 kcal/g of dextrose
      5) Glucose infusion rate (GIR)
         a) \[ \text{GIR (mg/kg/min)} = \frac{\text{IV rate (ml/hr)} \times \text{Dex concentr (g/dL)}}{\text{Weight (kg)}} \times 0.167 \]
         b) Start at GIR of 3–5 mg/kg/min
         c) Advance by 1–1.5 mg/kg/min or by D2.5% daily to max GIR 12–14 mg/kg/min
         d) Make adjustments based on Total Fluid Volume (TFV)
            i) Fluid restricted (PDA, Renal failure, Cardiac): Increase dextrose % to maintain same GIR
            ii) Higher fluid volumes (ostomy, short bowel syndrome): decrease dextrose % to maintain same GIR
         e) Consider insulin if not meeting nutritional goal because of hyperglycemia
            i) Increases cellular glucose uptake → Provides appropriate non-protein calories and prevents glucose conversion to fat
   b. Protein
      1) Amino Acids: Given as trophamine
         a) Neonatal form based on amino acid composition of breast milk
            i) Older formulations caused metabolic acidosis due to high concentration of nonessential AA
         b) Provides protein calories to attain positive nitrogen balance, prevent catabolism and stimulate growth
         c) Allows lower dextrose concentration preventing hyperglycemia
         d) Caloric density: 4 kcal/g of protein
         e) In NICU, can start from 1st day of life
            i) If no AA given, lose 1% body protein stores per day
            ii) 3.5 g/kg/day needed to meet intrauterine accretion rate
               a) Can start at 2.5 g/kg/day and advance by 0.5 g/kg/day
               b) Tolerated well, without adverse effects
                  1) No increase BUN/Cr, replaces urinary losses
   c. Fats
      1) Lipids: Provided as intralipid (IL) 20%
         a) Omega 6, Soybean oil-based
         b) Other formulations not approved in US: Fish oil, SMOF (mixture of soybean oil, MCT, olive oil, fish oil)
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c) Intralipid 10 vs 20%
   i) 10% more volume needed to provide same amount of fat
   ii) 10% higher phospholipid to TG ratio, which interferes with TG clearance

d) Provides non-protein calories (40%) for energy expenditure

e) Allows lower dextrose concentration, preventing hyperglycemia

f) Most caloric dense macronutrient = 9 kcal/ g

g) Usually started at 0.5–1 g/kg/day and increase by 0.5 g/kg/day daily to goal
   i) Monitor TG level when advancing
      (a) Keep triglyceride serum level <150 mg/dL
         (1) May have to decrease for a few days
         (2) Can add carnitine (see below)

h) Discontinue lipid infusion in the setting of infection
   i) Fats impair the macrophage activation system

i) Essential Fatty Acid Deficiency
   i) Deficiency of Linoleic and Linolenic acids (Omega 6)
      (a) Cannot be synthesized by humans
   ii) Presents with:
      (a) Dermatitis
      (b) Thrombocytopenia
      (c) Susceptibility to infection
      (d) Failure to Thrive
      (e) Abnormal brain and eye development
   iii) Can present as early as 1 week without fat supplementation
   iv) Minimum requirement 0.5 g/kg/day of fat

d. Vitamins (MVI)
   1) Pediatric MVI given based on weight
   2) Vitamin A
      a) Important for vision, normal lung development, immunocompetency
      b) Lost by binding to PN bag/tubing and exposure to light
      c) Vitamin A can be given by intermittent IM injection
   3) Vitamin E
      a) Free radical scavenger/antioxidant
         i) Prevents peroxidation of cell membrane (PUFA)
      b) May reduce incidence and severity of BPD and retinopathy of prematurity

4) Vitamin D
5) Vitamin K
6) Water-soluble vitamins

e. Electrolytes
   1) Na, K, Cl
      a) In NICU, not generally required first 24 hours
      b) Add after 1st 24–48 hours (diuresis occurs)
      c) Adjust thereafter based on laboratory testing
      d) usual requirements for Na, K, and Cl are 2-4 mEq/Kg/day.
         Take into account electrolyte content of other intravenous fluids and medications

2) Acetate
   a) Metabolic acidosis common in:
      i) Pre-term infants
         (a) Acidosis very common during sepsis, heart failure, PDA
         (b) Decreased renal reabsorption of HCO₃⁻ in the immature kidney
      ii) Short Bowel Syndrome
         (a) Increased losses of HCO₃⁻ (stools)
      iii) Trophamine contains AA which may be acidic (cysteine)
3) Calcium
   a) Hypocalcemia is a significant problem in preterm infants
      i) Maternal to fetal transfer of Ca occurs last trimester
      ii) Impaired response to PTH
      iii) Increased urinary loss
   b) In chronic PN patients, calcium supplementation is important to prevent metabolic bone disease

4) Phosphate
   a) Can be elevated in preterm infants, but usually corrects with increasing GFR
   b) In chronic PN patients, important to prevent metabolic bone disease
   c) Ca:Phos ratio of most PN solutions should be 1.7

5) Magnesium
   a) preterm infants whose mothers have received magnesium during labor may be hypermagnesemic. Withhold Mg from PN solutions until serum level is normal
   f. Other Additives
      1) Trace elements: selenium, zinc, chromium, manganese and copper
      2) Preterm infants have very low stores of trace elements at birth as accretion usually occurs in the 3rd trimester
      3) Cysteine
         a) Conditionally Essential AA especially in preterm infants
         b) Cysteine precipitates on standing so is added to PN just before administration
         c) Cysteine lowers the pH of PN solutions and making Ca and Phos more soluble and potentially causing metabolic acidosis
         d) Cysteine solutions contain chloride and add to total daily chloride intake
      4) Carnitine
         a) Conditionally Essential AA in preterm infant, and in, liver and metabolic disease
         b) Intermediary of fat metabolism
            i) Shuttles LCFA into mitochondria for b-oxidation
         c) Crucial for energy production in tissues dependent on fatty acid oxidation
            i) Cardiac and skeletal muscle
            ii) Not available in PN formulations
         d) Consider supplementation 10–20 mg/kg/day in preterm infants, PN >2 weeks, high TG, hypoglycemia, low serum carnitine level
         e) No study has shown positive effects of additive, but no ill effects
      5) Medications
         a) Some meds are not compatible with PN. Hold PN during their infusion.
            i) Acyclovir, amphotericin B, flagyl, bactrim
         b) Some meds can be added directly to PN bag
            i) Ranitidine/Famotidine, vitamin K, iron dextran, albumin

6. PN-Associated Liver Disease
   a. Etiology
      1) Thought to be multifactorial including characteristics of PN (composition, delivery) and characteristics of the patient
         a) Lipids currently heavily investigated: specifically, phytosterols in omega-6 formulations
            i) Phytosterols alter biliary canalicular membrane
            ii) Proinflammatory
         b) High dextrose concentration → steatosis
         c) Enteral starvation reduces bile flow and secretion of GI hormones
   b. Manifestations depends on age
      1) Infants: cholestasis
      2) Children/Adults: steatosis/steatohepatitis
      3) Both: biliary sludge, cholelithiasis
   c. Presentation
      1) Mild hepatomegaly → Increased Bili within 2–3 weeks
      2) Transaminitis, Alk Phos/GGT elevation later
      3) Can lead to cirrhosis
d. Histology
   1) Nonspecific
      a) Intracellular and canalicular cholestasis
      b) Interlobular bile duct proliferation
      c) Portal and lobular inflammation (minimal)
      d) Portal Fibrosis → Lobule → Bridging → Cirrhosis

e. Treatment
   1) Wean PN as soon as possible
   2) Decrease intralipid volume
   3) Consider Omegaven
      a) Fish oil (omega-3) based formulation
      b) Composed of long-chain polyunsaturated fatty acids
         i) DHA (docosahexaenoic acid), EPA (eicosapentaenoic acid)
      c) Initially made as an additive due to minimal quantities of essential
         fatty acid
      d) Discovered to improve cholestasis
      e) Not FDA approved
   4) Cycling of intralipids
   5) Actigall 10 mg/kg/day QD-TID

II. Monitoring Laboratory Parameters (see Table 1)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Early</th>
<th>Later</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, I/Os., TFV</td>
<td>Daily</td>
<td>Weekly</td>
<td>Biweekly-Monthly</td>
</tr>
<tr>
<td>Urine dip, Dex</td>
<td>q6</td>
<td>Daily</td>
<td>N/A</td>
</tr>
<tr>
<td>BMP</td>
<td>3x/week</td>
<td>Weekly</td>
<td>Biweekly-Monthly</td>
</tr>
<tr>
<td>Ca, Mg, Phos</td>
<td>Weekly</td>
<td>Weekly</td>
<td>Biweekly-Monthly</td>
</tr>
<tr>
<td>Serum Protein/Albumin</td>
<td>Weekly</td>
<td>Weekly</td>
<td>Biweekly-Monthly</td>
</tr>
<tr>
<td>LFT, DB</td>
<td>Weekly</td>
<td>Weekly</td>
<td>Monthly</td>
</tr>
<tr>
<td>TG/Chol</td>
<td>2–3x/week</td>
<td>Weekly</td>
<td>Monthly</td>
</tr>
<tr>
<td>Calories</td>
<td>Daily</td>
<td>Monthly</td>
<td>Biweekly-Monthly</td>
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</table>

III. Monitoring Anthropometric Measurements (see Table 2)

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>7 days</td>
</tr>
<tr>
<td>Length/Stature</td>
<td>4/8 weeks</td>
</tr>
<tr>
<td>Head Circumference</td>
<td>7 days (Infant)/4 weeks (up to 4 years old)</td>
</tr>
</tbody>
</table>
IV. Caloric Requirements
   A. Caloric recommendations are based on maintenance
      1. May need more for catch up
   B. PN caloric requirement is ~85% of enteral requirements
      1. Less fecal loss, bypass digestion
   C. Preterm: to continue Intrauterine Growth Accretion
      1. EN= 100–130 kcal/kg/day, including 3–3.5 g/kg/day Fat
      2. PN= 80–90 kcal/kg/day, including 3–3.5 g/kg/day Protein
   D. Children: can use general guidelines and/or metabolic equations
      1. General Guidelines
         a. Total Non Protein Calories= 60% CHO, 40% Protein
         b. Total Calories= 55% CHO, 30% Protein, 15% Fat
         c. >5 years old 1,500 cal/d (1st 20 kg) + 25 cal/kg/day for each additional kg
         d. By age: (Table 3)

Recommended Reading


Section 8 - Nutrition

80. Nutritional Consequences of Cholestasis

Juliana Frem, MD

I. Overview
Protein energy malnutrition occurs in about 60% of children with chronic cholestatic liver disease. Manifestations include growth failure, wasting and specific nutritional deficiencies resulting from anorexia, malabsorption of fat and fat-soluble vitamins, abnormal intermediary protein and carbohydrate metabolism, and increased metabolic demands associated with chronic disease and recurrent infection. Nutritional assessment should be a part of every medical encounter in cholestatic children including weight and height for age, weight for height and BMI. In some children with cholestasis and/or chronic liver disease with portal hypertension, body weight does not accurately reflect nutritional status. Serial measurements of triceps skinfold thickness and mid-arm circumference can be used to estimate body fat and muscle bulk, respectively. Clinicians should obtain a detailed feeding history and screen for signs and symptoms of vitamins and trace element deficiencies.

II. Etiologies of malnutrition in chronic cholestasis
A. Decreased food intake:
   1. Anorexia results from altered amino acid metabolism and elevated plasma tryptophan levels
   2. Altered taste perception results from zinc, magnesium and/or vitamin A deficiency
   3. Early satiety may result from mechanical compression of the viscera by ascites and/or organomegaly
   4. Nausea and vomiting may be caused by inflammatory cytokines or medications
   5. Frequent intercurrent illnesses decrease intake
B. Impaired nutrient digestion and absorption
   1. Reduced luminal bile concentration causes impaired intraluminal lipolysis, solubilization and absorption of long-chain triglycerides with resultant malnutrition and fat-soluble vitamin deficiency
   2. Vascular congestion secondary to portal hypertension can result in an edematous enteropathy that produces nutrient malabsorption
   3. Small bowel bacterial overgrowth in patients with previous Kasai portoenterostomy causes bile salt deconjugation and abnormal micelle formation
C. Increased energy requirements result from:
   1. Underlying liver disease processes such as inflammation
   2. Recovery from major insults such as infection or surgery
   3. Increased respiratory effort secondary to ascites or organomegaly
D. Altered fuel consumption
   1. May produce negative protein balance
   2. May decrease hepatic glycogen stores
   3. May cause an increased used of fat stores as a substrate for metabolism, a pattern seen in starvation

III. Nutritional consequences of chronic cholestasis
A. Carbohydrates
   1. Fasting hypoglycemia: abnormal hepatocyte function and reduced hepatocyte mass results in impaired gluconeogenesis and reduced glycogen stores
   2. Postprandial hyperglycemia and reduced glucose utilization may be caused by impaired catabolism of insulin in the liver
B. Proteins
   1. Negative nitrogen balance results from impaired hepatic protein synthesis and increased use of amino acids for gluconeogenesis in the presence of disordered carbohydrate metabolism
   2. Reduced synthesis of insulin-like growth factor-1 and its binding protein results in growth hormone resistance
C. Fats
1. Reduced fat stores occur secondary to increased fat oxidation and fat malabsorption
2. Impaired micelle formation results in malabsorption of long-chain triglycerides, fat-soluble vitamins (A, D, E and K) and essential fatty acids
3. Linoleic and linolenic acids are essential fatty acids used in synthesis of long-chain polyunsaturated fatty acids (LCPUFAs). LCPUFAs such as arachidonic acid and docosahexaenoic acid are essential for neurologic development and growth in children
4. Medium-chain triglycerides (MCT) are more water soluble than long-chain triglycerides and are readily absorbed by the intestinal mucosa, making them a better source of fat calories in cholestatic children

D. Vitamin A
1. Retinyl palmitate and carotenoids are derived from animal and plant sources, respectively
2. Deficiency in vitamin A results in night blindness, xerophthalmia and keratomalacia
3. Vitamin A may play a role in immune function as suggested by decreased morbidity of diarrheal illnesses, measles, and HIV infection with vitamin A supplementation
4. Serum retinol level is a convenient, clinically practical measure of vitamin A nutrition. Retinol dose response is more reliable and is based on a sharp increase of retinol level in response to vitamin A administration in patients who are deficient in vitamin A
5. Treatment: refer to Table 1.

E. Vitamin D
1. There are two major prohormones of vitamin D—vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Prohormones first undergo 25-hydroxylation in the liver (25-hydroxy vitamin D) and then further hydroxylation in the kidney, producing 1,25 dihydroxy vitamin D or 24, 25 dihydroxy vitamin D
2. Food rich in vitamin D include fish oils and fortified dairy products, although adequate amounts can be synthesized in the skin when cholesterol is exposed to sufficient ultraviolet B light
3. Deficiency results in defective bone mineralization
4. Measurement of serum 25-hydroxy vitamin D is the most accurate means of assessment of vitamin D status. Half-life of 1,25 dihydroxy vitamin D is so short that it is a poor reflection of chronic vitamin D status
5. Treatment: refer to Table 1.

F. Vitamin E (α-tocopherol)
1. Group of tocopherols of which α-tocopherol is the most studied. Vitamin E is found in nuts, green leafy vegetables and vegetable oils
2. Deficiency associated with progressive neuromuscular syndrome with areflexia, cerebellar ataxia, posterior column dysfunction and peripheral neuropathy. Hemolytic anemia occurs due to oxidative damage to red blood cells
3. In cholestasis, total serum vitamin E levels may be artificially elevated even in deficient children, because vitamin E concentrates in the increased lipid fraction of serum
4. The most reliable index of vitamin E status is the ratio of serum vitamin E (mg/dL) to total serum lipids (g/dL). In infants and children <12 years of age, vitamin E to total serum lipid ratio <0.6 mg/g indicates vitamin E deficiency
5. Treatment: refer to Table 1

G. Vitamin K
1. Vitamin K1 is abundant in green leafy vegetables, dairy products, and liver. Vitamin K2 is derived from bacterial metabolism in the gut. Bacterial production of vitamin K2 is not sufficient in the absence of dietary vitamin K1
2. Deficiency causes abnormal coagulative function. Vitamin K is required for carboxylation of glutamic acid residues on coagulation factors II, VII, IX, X and proteins C and S in the liver
3. Osteocalcin requires vitamin K-dependent carboxylation, hence the link between vitamin K deficiency and bone disease
4. Confirmation of vitamin K deficiency can be made by noting the improvement of a prolonged prothrombin time after a parenteral dose of vitamin K
5. The PIVKA (or proteins induced in vitamin K absence)-II assay is a more sensitive but not widely available measure of vitamin K status
6. Treatment: refer to Table 1
H. Folic acid
1. In severe hepatic insufficiency, the liver cannot methylate folic acid, resulting in deficiency of the active vitamin

I. Trace elements
1. Calcium and magnesium metabolism are closely related to vitamin D status. Depletion of minerals occurs in cholestasis because of reduced vitamin D-stimulated intestinal absorption. Both also become bound to unabsorbed fatty acids in the gut, further reducing absorption.
2. Iron deficiency can occur in the presence of reduced intake or overt losses from gastrointestinal bleeding in patients who have portal hypertension.
3. Elevated levels of copper and manganese may occur, because these metals are primarily excreted in bile.

IV. Nutritional management
A. The goal for caloric intake should be 125%–150% of recommended dietary allowance based on ideal body weight (50th percentile of weight-for-height measurement). Anthropometric measurements may be more appropriate to guide nutritional therapy.
B. Adequate protein intake is necessary (2.0–3.0 mg/kg/d in small infants) while delivering optimal energy intake.
C. Infants should be started on a formula containing MCT oil. The formula may be concentrated to provide 24 kilocalories per ounce.
D. Older children can add calorie-dense nutritional supplements to their usual diet. Glucose polymers or MCT oil can be added to solid food.
E. If oral intake is not sufficient, patients may be started on supplemental enteral feedings.
F. Essential fatty acid deficiency must be suspected in the cholestatic child with poor growth, dry scaly rash, or thrombocytopenia. Corn oil, safflower oil, or lipid emulsions can be added to formula to provide additional linoleic acid, if needed.
G. Refer to Table 1 for specific vitamins supplementation. Vitamin status should be monitored every 3–6 months and supplementation should continue at least 3 months after resolution of jaundice.

<table>
<thead>
<tr>
<th>Vitamin/trace element</th>
<th>Treatment/prevention</th>
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</thead>
<tbody>
<tr>
<td>Vitamin A</td>
<td>5,000–25,000 U/d of water-soluble preparation</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Vitamin D3 3,000–5,000 U/d</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>15–25 IU/kg per day of a water-soluble form of vitamin E, d-α-tocopherol polyethylene glycol 1000 succinate (TPGS)</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>2.5–5.0 mg 2–7x per week</td>
</tr>
<tr>
<td>Zinc</td>
<td>1–2 mg/kg/d of elemental zinc</td>
</tr>
<tr>
<td>Calcium</td>
<td>25–100 mg/kg/d of elemental calcium</td>
</tr>
</tbody>
</table>

Recommended Reading


