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Objectives

After completing this article, readers should be able to:

1. Understand the physiology and pathophysiology of malabsorption.
2. Describe the various manifestations of malabsorption.
3. Recognize the extensive differential diagnosis for malabsorption.
4. Plan an investigative approach for children who present with symptoms suspicious for malabsorption.

Introduction

The primary function of the small intestine is digestion and absorption of ingested nutrients. The term malabsorption refers to impairment in the absorption of one or more substances by the small intestine.

Malabsorptive disorders include numerous clinical entities that may result in chronic diarrhea, abdominal distention, and failure to thrive. Although diarrhea is a key feature of malabsorption, it may not be apparent at presentation; the only symptom may be poor growth. The pediatrician must be able to recognize the various manifestations of malabsorption (Table 1) to establish an early diagnosis and initiate treatment with the aim of avoiding long-term complications of malnutrition. It becomes necessary, therefore, for the physician to understand the physiology and pathophysiology of digestion and absorption.

Most nutrients cannot be absorbed in their natural form and need to be digested. Food is chemically reduced by various enzymes to digestive end products small enough to participate in the absorption process, which then are transported across the intestinal epithelium by active transport, passive transport, facilitated diffusion, or endocytosis. Disruption of these physiologic stages can lead to maldigestion, malabsorption, or both.

Physiology and Pathophysiology of Digestion and Absorption

Carbohydrates

Beyond infancy, starch makes up much of the ingested carbohydrates. In small amounts, lactose and sucrose make up the rest. Much ingested starch is found in wheat, rice, and corn as polysaccharides. The two chief constituents of starch are amylose, which is nonbranching in structure, and amylopectin, which has highly branched chains. Of the carbohydrates present in the diet, only starches require preliminary luminal digestion by salivary, and more importantly, pancreatic amylases, which act on interior alpha-1,4 glucose-glucose links of starch, releasing maltose, maltotriose, and alpha-limit dextrins, which are branched glucose polymers. Despite the slow development of pancreatic amylase, whose secretion reaches adult levels during the second year after birth, starch malabsorption is rare in infants because of the activity of the brush border-bound glucoamylase that develops early in life.

The final stages of carbohydrate digestion occur by specific enzymes located in the brush border of intestinal epithelial cells. These enzymes, primarily sucrase-isomaltase that breaks down maltose and isomaltose into glucose and sucrose into glucose and fructose, lactase that splits lactose into glucose and galactose, and glucoamylase that releases glucose from glucose polymers, are present in the highest concentration at the villous tips in the jejunum and persist throughout most of the ileum. The final three monosaccharides, glucose, galactose, and fructose, enter enterocytes through carrier-mediated transport.

In malabsorption, maldigested oligosaccharides and unabsorbed monosaccharides are

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Table 1. Signs and Symptoms of Malabsorption

- Weight loss
- Failure to thrive
- Diarrhea
  - –Loose and watery due to carbohydrate, bile acids, or fatty acids malabsorption
  - –Bulky and foul-smelling due to fat malabsorption
- Abdominal pain
- Abdominal distention
- Anemia
- Increased flatulence
- Edema
- Osteomalacia
- Bleeding tendencies

emptied into the colon, where they draw water into the lumen due to their osmotic effect. Colonic bacteria then may ferment the maldigested oligosaccharides and unabsorbed monosaccharides, leading to the production of gases such as carbon dioxide, hydrogen, and methane, as well as acids such as acetic, butyric, propionic, and lactic. Hence, the stool usually is watery and acidic, with significant amounts of unabsorbed reducing sugars. A noninvasive test known as the hydrogen breath test quantifies the amount of hydrogen produced by gut fermentation in exhaled air. The breath content of hydrogen correlates with the degree of malabsorption of the ingested carbohydrate.

Carbohydrate malabsorption may be due to mucosal damage, short bowel syndrome, or congenital intestinal transport or enzyme deficiencies. It also can be related to excessive ingestion of juices that contain universally malabsorbed sugars such as sorbitol. The most common type of carbohydrate malabsorption is lactose malabsorption due to "adult-onset" lactase deficiency. Although congenital lactase deficiency is rare, reported mostly in Finland, the "adult-onset" form is very common, beginning as early as 2 years of age in some racial groups. Its prevalence can reach 80% to 100% in Asians, African Americans, and families of Mediterranean ancestry. It has been postulated that a genetically controlled "switching off" of the lactase gene occurs in susceptible individuals. Although lactase does not function as an inducible enzyme, continued exposure to milk products beyond infancy can, to a certain degree, delay the age of onset of symptoms in people who have genetically determined lactase deficiency.

Brush border enzyme deficiencies can follow injury to the small intestinal mucosa caused by disorders such as infectious gastroenteritis, gluten-induced enteropathy, or cow milk protein sensitivity. Glucoamylase is the most resistant of the disaccharidases to small bowel damage and, therefore, often is the last of the disaccharidases to be lost in small bowel injury, allowing glucose polymer digestion to continue or recover quickly. Lactase, on the other hand, is the most sensitive to injury, and its recovery may take months. This finding has popularized the use of formulas containing sucrose or glucose polymers for infants and lactose restriction in children recovering from gastroenteritis.

Sucrase-isomaltase deficiency is the most common congenital enzyme deficiency that causes carbohydrate maldigestion. It was described first in 1961 by Weijers and colleagues. It is a rare condition but can be as prevalent as 5% in Greenlanders. The deficiency can present with diarrhea, bloating, and cramps in infancy when sucrose-containing fruits are introduced or can manifest as intermittent symptoms in an older child. The diagnosis is established when a histologically normal duodenal or jejunal biopsy demonstrates deficient sucrase-isomaltase activity. Treatment is strict avoidance of sucrose or the use of the commercially available preparation of sucrase before any sucrose ingestion.

Glucose and galactose are two monosaccharides that are absorbed via energy-dependent specific carrier proteins known as SGLT1. In glucose-galactose malabsorption, the sodium-coupled mucosal uptake of glucose is absent or severely impaired. Fortunately, this congenital defect is very rare.

Proteins

Digestion of proteins begins in the stomach under the influence of pepsin, but gastric proteolysis is limited. The bulk of dietary protein is hydrolyzed by pancreatic proteases, proteases in the brush border of intact epithelial cells, and peptidases within the cytoplasm of intestinal cells. Pancreatic proteases normally are secreted into the duodenal lumen in the inactive form. Enterokinase, a glycoprotein anchored in the enterocyte brush border of the proximal small bowel, activates the pancreatic proteases into endopeptidases (trypsin, chymotrypsin, elastase, DNAase, and RNAase) and exopeptidases (carboxypeptidases A and B), which hydrolyze proteins into amino acids (AAs) and oligopeptides. Brush border peptidases then digest the oligopeptides into di-, tri-, and tetrapeptides that, along with the generated AAs, can be absorbed into the enterocyte, where peptides can be hydrolyzed further by cytoplasmic peptidases.

Thus, protein malabsorption leading to failure to thrive, hypoproteinemia, and edema can be seen in pan-

creatic insufficiency, enterocyte deficiency, and impaired AA or peptide transport by the enterocyte. A fecal elastase test is a good screening test for protein maldigestion due to pancreatic insufficiency. Analysis of duodenal fluid for pancreatic enzyme activity following secretin stimulation is a more definitive method of diagnosing pancreatic enzyme deficiency but requires endoscopy. A number of patients who have inflammatory enteropathies leading to malabsorption, such as Crohn disease and celiac disease, may present with increased loss of fecal protein nitrogen through transudation of protein across inflamed mucosa, a state referred to as protein-losing enteropathy (PLE). PLE is not a discrete clinical entity but rather a manifestation of a wide variety of gastrointestinal and extraintestinal diseases that can lead to abnormal protein leakage across the gut or diminished uptake by intestinal lymphatics. Alpha-1-antitrypsin is a serum protein that has a molecular weight similar to that of albumin, is synthesized by the liver, is not ingested in the diet, is relatively resistant to digestion, and is stable for 72 hours in a stool sample. Accordingly, measuring fecal clearance of alpha-1-antitrypsin is an accurate method of documenting gastrointestinal protein loss, but it requires a 24-hour stool collection and a serum sample. A random measurement of fecal alpha-1-antitrypsin is used more commonly as a screening test for PLE. Other features of protein deficiency include recurrent or severe infections, muscle atrophy, weakness, hair loss, and irritability.

Lipids

Pancreatic enzymes measured in term and preterm newborns have only trace amounts of lipase and no amylase. By 2 years of age, the basal activity and secretory response of pancreatic lipase become well developed. Thus, fat digestion in newborns depends primarily on the activities of lingual lipase, gastric lipase, and a specific digestive lipase present in human milk. With age, however, pancreatic lipase and colipase become more important in fat digestion, breaking down ingested fat into fatty acids and monoglycerides. These products, however, are insoluble. They are rendered water-soluble through micelle formation with bile acids, which are synthesized in the liver from cholesterol and secreted into bile.

Once formed, micelles enter the enterocyte at the luminal surface of the brush border, mostly by passive diffusion. Once inside the enterocyte, long-chain fatty acids are transported to the endoplasmic reticulum where they are re-esterified to triglycerides that, together with phospholipids, cholesterol, and protein, are assembled into lipoproteins (chylomicrons and low-density lipoproteins). Such lipoproteins are excreted by reverse pinocytosis into the intercellular space, from which they enter the lymphatics and the systemic circulation. Medium- and short-chain fatty acids are more water-soluble and are absorbed directly into the portal blood system.

Fat maldigestion or malabsorption results in a variety of manifestations due not only to malassimilation but also to fat-soluble vitamin (A, D, E, and K) deficiency. Generally, fat malabsorption deprives the body of energy, leading to weight loss and malnutrition. Unabsorbed fatty acids irritate colonic mucosa, resulting in diarrhea. Stools usually are large, pasty, and greasy (steatorrhea). They tend to float in toilet water because of the increased gas content. In addition, fatty acids in the intestine can bind calcium, leaving oxalate free to be readily absorbed. Hence, patients are at increased risk for oxaluria and calcium oxalate kidney stones.

Fat malabsorption occurs in pancreatic insufficiency, which can be congenital, such as in cystic fibrosis and Shwachman-Diamond syndrome, or acquired, as in chronic pancreatitis. Fat malabsorption also occurs in diseases that impair bile production or excretion and in abetalipoproteinemia, an autosomal recessive disorder in which failure to form apolipoprotein in the enterocyte leads to lipid inclusions in the villous epithelium. Patients born with abetalipoproteinemia tend to have low serum cholesterol concentrations (<50 mg/dL [1.3 mmol/L]) and progressive neurologic deterioration, with ataxia and ophthalmoplegia due to chronic vitamin E deficiency.

Vitamins and Minerals

Diseases causing malabsorption of dietary fat commonly cause malabsorption of fat-soluble vitamins, resulting in a variety of symptoms. Vitamin A deficiency is associated with follicular hyperkeratosis; vitamin E deficiency leads to a progressive demyelination of the central nervous system, resulting in various neurologic symptoms. Malabsorption of vitamin D leads to osteopenia and rickets, and malabsorption of vitamin K is associated with easy bruising and bleeding.

Vitamin B12 (cobalamin) is liberated from food and binds haptocorrin (R binder) at an acid pH. The complex migrates along with free gastric intrinsic factor to the duodenum, where, in the presence of bicarbonate, pancreatic proteases hydrolyze the R binder and liberate cobalamin. Free vitamin B12 becomes available to bind to gastric intrinsic factor. The newly formed complex traverses down the small intestine to the ileum, where it is actively absorbed. Cobalamin then is transported in blood bound to transcobalamin, a circulating transport protein. Although pancreatic insufficiency can lead to vitamin B12 deficiency, the lack of intrinsic factor is the most common cause of vitamin B12 deficiency. Ileal

resection or inflammation as well as congenital absence of transcobalamin are some of the other causes of vitamin B12 deficiency. Cobalamin deficiency, if severe, can lead to megaloblastic anemia and irreversible damage to the nervous system, including subacute combined degeneration of the spinal cord.

Zinc malabsorption can occur in mucosal disease of the small intestine as well as in acrodermatitis enteropathica, a condition in which patients lack the cofactor necessary for its absorption. Patients present with hypogeusia (reduced ability to taste), dermatitis involving the perioral and perianal skin and distal extremities, failure to thrive, chronic diarrhea, edema, and alopecia. Treatment with zinc sulfate produces a dramatic clinical recovery.

Specific Disorders Leading to Malabsorption

Pancreatic Insufficiency

Cystic fibrosis (CF) is a major cause of pancreatic exocrine failure in children. It is an autosomal recessive disorder caused by a mutation in the *CFTR* gene on chromosome 7, leading to defective chloride channel function. This defect results in generalized dysregulation of salt and water flux across epithelial glandular cells. The disease normally involves numerous organs and presents with varied clinical symptoms. Even though pulmonary disease is the major cause of morbidity and mortality, most patients (85%) have pancreatic insufficiency and suffer from gastrointestinal symptoms. Clinical signs of pancreatic insufficiency develop when less than 10% of normal pancreatic enzyme activity is present in the duodenum. Patients who have CF and pancreatic insufficiency usually present before 6 months of age with failure to thrive. The stools are bulky or sometimes loose. Energy and protein loss in the stool prevents normal growth and may be associated with hypoalbuminemia, edema, and anemia.

Patients are treated with oral pancreatic enzyme replacement derived from processed porcine pancreas. Enzymes are administered as 500 to 1,500 units of lipase per kilogram per meal, depending on the age of the patient, and are adjusted upward based on stool pattern and weight gain. However, doses should not exceed 2,500 lipase units per kilogram per meal to decrease the risk of developing fibrosing colonopathy, a condition seen in patients who have CF and receive high-dose pancreatic enzyme supplementation. Fat-soluble vitamin supplements are given routinely to those who have CF. Some children continue to be symptomatic with fat malabsorption despite taking appropriate doses of enteric-coated enzymes; they can benefit from gastric acid suppression with histamine-2 blockers or proton pump inhibitors, which can optimize the intraluminal action of the supplemental enzymes.

Other causes of pancreatic insufficiency include chronic pancreatitis, Shwachman-Diamond syndrome, Johanson-Blizzard syndrome, and Pearson syndrome (Table 2). Shwachman-Diamond syndrome, the second most common cause of pancreatic insufficiency, is an autosomal recessive disorder characterized by exocrine pancreatic failure, skeletal abnormalities, and bone marrow dysfunction, primarily cyclic neutropenia. Pancreatic insufficiency in this condition probably is due to failure of acinar tissue to develop normally in utero. Pancreatic tissue is replaced by fatty deposition. Over time, however, pancreatic hypoplasia is reversed, and there is an increase in normal pancreatic tissue volume, along with possible improvement in pancreatic function. Johanson-Blizzard syndrome is characterized by hypoplasia of the alae nasi, deafness, imperforate anus, urogenital malformations, and dental anomalies. As with Shwachman-Diamond syndrome, the pancreas is replaced with fatty tissue. Endocrine abnormalities such as diabetes and hypothyroidism have been associated with this condition. Pearson syndrome, on the other hand, results from deletions in mitochondrial DNA. Patients have pancreatic insufficiency and refractory sideroblastic anemia. Death frequently ensues in infancy or early childhood due to sepsis or metabolic disarray.

Defects in Bile Acid Micellar Solubilization

Moderate steatorrhea can occur in any hepatobiliary disorder leading to bile acid deficiency (Table 3), which can result from impaired hepatic synthesis or impaired bile flow. Increased enteric bacterial deconjugation, reduction in ileal reabsorption due to inflammation or resection, or the presence of medications that bind bile acids also can lead to bile acid deficiency. Patients present with failure to thrive and fat-soluble vitamin deficiencies.

Bile acids usually are recycled through the enterohepatic

Table 2. Pancreatic Causes of Malabsorption

- Cystic fibrosis
- Shwachman–Diamond syndrome
- Johanson–Blizzard syndrome
- Pearson syndrome
- Chronic pancreatitis
- Trypsinogen deficiency
- Amylase deficiency
- Lipase deficiency

Table 3. Conditions Leading to Bile Acid Deficiency

- Bile acid deconjugation by bacteria
- Chronic cholestasis
- Bile acid pool depletion
- Ileal resection

circulation. Many factors can prevent such recirculation, but bacterial overgrowth of normal or abnormal flora is the most common cause of altered intraluminal metabolism of bile acids. Anaerobes and *Staphylococcus aureus* deconjugate bile acids, thus impeding their active reabsorption by the terminal ileum into the portal circulation for reuptake by the liver. Deconjugated bile acids directly inhibit the carbohydrate transporters and damage enterocytes. They also may stimulate the colon to secrete fluid, contributing to diarrhea.

Intestinal Brush Border Disorders

Intestinal brush border disorders include congenital defects in villous structure, acquired disorders that reduce mucosal surface area, and inflammatory disorders leading to villous atrophy (Table 4). Patients born with congenital disorders present with symptoms in the newborn period. Microvillus inclusion disease is characterized by massive, watery diarrhea and severe villous atrophy with periodic acid-Schiff (PAS)-staining secretory granules in the crypt and villous epithelium. Morphologic abnormalities are seen in the small and large bowels. In Tufting disease, on the other hand, the villous atrophy is moderate and localized to the small bowel. Treatment for both conditions entails long-term parenteral nutrition and, ultimately, small bowel transplantation.

Table 4. Brush Border Disorders

Congenital Causes

- Microvillus inclusion disease
- Tufting disease
- Primary lactase deficiency
- Sucrase-isomaltase deficiency
- Glucose/galactose malabsorption
- Enterokinase deficiency
- Hartnup disease
- Lowe syndrome
- Lysinuric protein intolerance

Reduced Mucosal Surface Area

- Short bowel syndrome
- Ileal resection (such as necrotizing enterocolitis or Crohn disease)

Inflammatory Causes

- Celiac disease
- Crohn disease
- Infection
- Postinfectious diarrhea
- Allergic enteropathy
- Autoimmune enteropathy

Surgical resection of the bowel, usually performed for congenital malformations or irreversible injury to the gastrointestinal tract (Table 5), leads to short bowel syndrome (SBS), the classic example of a malabsorptive disease due to reduced surface area. Children and adults who retain 30% or less of normal small intestinal length after resection (about 70 cm in infants and 150 to 200 cm in adults) are at increased risk of developing SBS. Diarrhea results primarily when aggregate secretion by the remnant proximal bowel exceeds absorptive capabilities of the remnant distal bowel. The region of bowel remaining after resection determines adequacy of assimilation, and the degree of malabsorption correlates with the length of remaining small bowel, its absorptive capacity, the presence or absence of the ileocecal valve and colon, and intestinal adaptation.

The primary objective in treating patients who have SBS is prevention of permanent intestinal failure by weaning them from parenteral nutrition. Hence, enteral nutrition is begun when postoperative ileus has resolved; upper gastrointestinal tract decompression has ended; and stable metabolic, fluid, and electrolyte status has been achieved. Early initiation of enteral nutrition, even if modest, is recommended to minimize the degree of mucosal atrophy.

Inflammatory villous injury may result from enteric infections such as acute viral infections or from allergic or

Table 5. Causes of Short Bowel Syndrome

Neonates

- Congenital malformations (gastroschisis, omphalocele, small intestinal atresia, volvulus due to malrotation)
- Necrotizing enterocolitis

Older Children and Adolescents

- Volvulus due to malrotation
- Trauma
- Intra-abdominal neoplasia
- Radiation enteropathy

immunologic responses to nutrients. Recovery from an acute infectious insult requires an intact immune system and appropriate nutrition support. If either is missing, a chronic diarrheal state ensues. Although *Giardia lamblia*, a protozoan, can infest healthy children chronically, such an infestation usually is more of a concern in immunodeficient children, particularly those who have selective immunoglobulin (Ig) A deficiency. Patients who have giardiasis experience diarrhea, steatorrhea, abdominal distention, abdominal pain, and even weight loss. The diagnosis usually is based on identification of the parasites in stool preparations through direct examination or antigen testing or by finding the organism on proximal intestinal biopsies. Giardiasis is more common in institutionalized patients, in child care settings, and among individuals drinking well water or swimming in lakes and streams. Although asymptomatic infection is common, treatment of asymptomatic carriers is not recommended.

Postinfectious diarrhea is the persistence of diarrhea beyond the expected duration of an infectious illness in a child who is otherwise in good health. Its pathogenesis is unclear, but it has been suggested that postinfectious diarrhea might be due to a delay in epithelial renewal, leading to a deficiency in mature villi and a decrease in brush border enzymes and transport carriers. The greatest risk factor for progression to postinfectious diarrhea in a child who has an acute diarrheal illness is pre-existing malnutrition that predisposes to delayed regeneration of crypt epithelium. Other risk factors are preschool age, reduced immune competence, and underlying systemic disease. Children often benefit from a high-calorie, low-lactose, moderate-fat, and high-starch diet; infants may require a protein-hydrolysate formula with medium-chain triglycerides and low lactose content.

Autoimmune enteropathy is a rare disorder characterized by severe and protracted watery diarrhea early in life that is not responsive to dietary restriction and is defined by the presence of circulating antibodies to enterocytes along with a duodenal mucosal biopsy that shows total villous atrophy and severe inflammatory cell infiltration of the lamina propria. Treatment consists of parenteral nutrition and immunosuppressive therapy.

Eosinophilic gastroenteropathy is characterized by prominent eosinophilic infiltration of variable depth at one or more gastrointestinal sites with or without peripheral eosinophilia. The entity is divided into three forms: mucosal, muscular, and serosal. Eosinophilic gastroenteropathy can be primary, also known as allergic, or due to one of many conditions that provoke eosinophilic inflammation, with parasitic infections being the leading cause. Patients often have heterogenous clinical presentations, with abdominal pain being the most common presenting complaint in the mucosal type, followed by nausea, vomiting, and diarrhea. Food sensitivity has been incriminated in some patients, but only a minority responds favorably to elimination diets. Systemic corticosteroids produce symptomatic and histologic improvement regardless of disease type.

Celiac disease is an immune-mediated enteropathy caused by permanent sensitivity to gluten in genetically susceptible individuals. Its prevalence is estimated to be 1 in 300 to 1 in 80 children. It should be considered in any child who has vomiting and diarrhea with failure to thrive, abdominal distention, dermatitis herpetiformis, dental enamel defects, short stature, delayed puberty, osteoporosis, and persistent iron deficiency anemia. Celiac disease also occurs in asymptomatic individuals who have type 1 diabetes, Down syndrome, Turner syndrome, Williams syndrome, and selective IgA deficiency and in first-degree relatives of individuals who have celiac disease.

Gluten protein is derived from a group of cereal grains that includes wheat, rye, and barley. Pure oats are not considered an offending agent, although oats in the United States usually are milled with other grains that contaminate the mixture with gluten and may cause problems. Patients sustain an autoimmune reaction to the gliadin protein fraction of gluten.

Tissue transglutaminase (TTG), an enzyme that modifies gluten peptides into a form that is resistant to proteolysis, may stimulate the immune system in genetically susceptible individuals, leading to the development of autoantibodies against it. This enzyme, therefore, is the autoantigen in celiac disease. Measurement of IgA antibody to human recombinant TTG is recommended for initial testing for celiac disease, along with quantitative serum IgA measurement, because approximately 1 in 8,500 of the general population can have celiac disease and IgA deficiency concurrently. The gold standard for diagnosis is a small bowel biopsy documenting villous injury. Because histologic changes in celiac disease can be patchy, multiple biopsies obtained from the second or more distal part of the duodenum are recommended. Once a diagnosis is made, the only scientifically proven treatment remains a gluten-free diet for life.

The presenting symptoms in Crohn disease can be subtle. However, almost two thirds of affected children present with weight loss. The cause of this poor nutritional status is complex; contributing factors include inadequate intake, malabsorption, altered energy demands, and losses through stool. Malabsorption can result from generalized small bowel mucosal injury, PLE, or rapid intestinal transit. Ultimately, the malabsorption leads to

vitamin and trace element deficiencies, delayed puberty, and growth failure. The principal goal of medical management is to induce disease remission to enable normal growth and development.

Transport Defects

Intestinal lymphangiectasia is characterized by dilated intestinal submucosal and subserosal lymphatics, diarrhea, steatorrhea, PLE, growth retardation, hypoalbuminemia, edema, and lymphopenia. The condition may be primary due to congenital abnormalities in the lymphatic vessels of the intestinal tract or secondary to a number of disorders such as congestive heart failure, post-Fontan procedure for hypoplastic left heart syndrome, liver cirrhosis, lymphatic tumors, or Behçet disease (Table 6). Perturbation of lymphatic flow results in malabsorption of fat-soluble vitamins and long-chain dietary fats. Medium- and short-chain fatty acids still can be absorbed and transported directly through the mesenteric venous blood to the liver. Poor lymphatic drainage, however, produces increased intestinal lymphatic pressure and leakage of lymph into the intestinal lumen, with consequent loss of proteins and lymphocytes. Patients can have generalized or even asymmetric edema. Chylous effusions have been described.

In addition to addressing the underlying cause in secondary intestinal lymphangiectasia, treatment for primary and secondary cases often includes a high-protein, low-fat diet, with the fat provided primarily in the form of medium-chain triglycerides. Octreotide has been helpful but probably should be reserved for patients who fail dietary therapy. Surgery is reserved for palliation of large chylous ascites or resection of isolated lesions. In cases of intestinal lymphangiectasia with PLE resulting from a Fontan procedure, medical management has included anticoagulation with subcutaneous high-molecular weight heparin to improve hemodynamics and stabilization of the intestinal cell membrane with high-dose steroids.

Diagnostic Investigations

A detailed history and physical examination and judicious use of laboratory studies usually provide the information necessary to diagnose a maldigestive or malabsorptive disorder (Table 7). The presence of diarrhea, defined as stool weight of more than 10 g/kg per day, as well as its timing of onset, character, and frequency, can offer clues to the cause (Table 8). However, stool color, odor, and the presence of undigested food particles are often of limited diagnostic value. Intake should be assessed carefully because dietary restriction can lead to malnutrition that, in turn, can lead to malabsorption. Family history can be helpful in diagnosing genetically determined disorders.

Malabsorptive disorders should be considered during the evaluation for failure to thrive, malnutrition, or delayed puberty, even in the absence of gastrointestinal tract symptoms. Measurement of height, weight, and head circumference; calculation of weight for length; and construction of a growth curve are fundamental elements of the physical examination. Lean body mass and body fat can be estimated and used to monitor response to therapy. Examination also should focus on

Table 6. Transport Defects

- Intestinal lymphangiectasia
- Whipple disease

Table 7. Initial Evaluation of Malabsorption

- Detailed history
- Complete physical examination
- Serial growth and anthropometric measurements
- Screening laboratory tests:
  - —Blood: Complete blood count, complete metabolic panel, erythrocyte sedimentation rate, tissue transglutaminase immunoglobulin A (IgA) antibody, total IgA
  - —Stool: Culture, ova and parasites, *Clostridium difficile* testing, occult blood, pH, reducing substances, fecal hydrolysis for detection of nonreducing carbohydrates, elastase, alpha-1-antitrypsin, stain for fat globules
- Other: Sweat chloride test

Table 8. Stool Characteristics

Color	
• Acholic suggests cholestasis	
Character	
• Greasy suggests fat malabsorption	
Timing of Symptoms	
• Neonatal period suggests congenital disorder	
• Following gluten initiation suggests celiac disease	
• Following fruit introduction suggests sucrase-isomaltase deficiency	
• After an acute infection suggests postinfectious diarrhea	

cutaneous and neurologic manifestations, evidence of respiratory disease or hepatomegaly, and findings on rectal examination.

Laboratory studies may help to confirm the presence of malabsorption and identify its cause. A stool sample can be analyzed for occult blood and fecal leukocytes, the presence of which can indicate an inflammatory condition; pH and reducing substances, which can reflect carbohydrate malabsorption; and qualitative fecal fat excretion or stain for fat globules, which is a screen for fat malabsorption. If an infectious cause is suspected, a stool sample should be submitted for bacterial culture and examination for ova and parasites.

A complete blood count can be used to screen for anemia, which is common in those who have malabsorption, as well as the associated neutropenia in Shwachman-Diamond syndrome, lymphopenia in intestinal lymphangiectasia, or acanthocytosis of abetalipoproteinemia. The use of total protein and albumin values can assess protein intake and loss. A fecal alpha-1-antitrypsin assessment can confirm PLE if elevated, and an abnormally low fecal elastase suggests pancreatic insufficiency.

If the initial evaluation results are inconclusive, second-phase testing can be initiated and can include a quantitative fat excretion test measured in a 72-hour stool collection, which can be used with a 72-hour dietary history to estimate fat malabsorption (Table 9). However, this test is not performed routinely because of the difficulty in collecting the 72-hour stool sample from a child. Carbohydrate malabsorption can be tested by using the breath hydrogen test, in which breath hydrogen content increases following ingestion of the suspected sugar. An early rise in hydrogen content after ingesting any carbohydrate suggests small bowel bacterial overgrowth. However, the lactulose breath hydrogen test is the test of choice for making this diagnosis.

Absorption of D-xylose is passive and independent of other digestive requirements. Approximately half of what is absorbed is metabolized; the remainder is excreted in the urine. Thus, a low serum concentration or timed urine excretion following the administration of a standard oral dose of D-xylose correlates with decreased mucosal surface area or permeability of the small bowel. In conditions associated with fat malabsorption, concentrations of vitamins A, E, and D and prothrombin time (to assess vitamin K adequacy) should be evaluated.

Endoscopy with small bowel biopsy is the gold standard for documenting villous injury and can offer a definitive diagnosis in many circumstances. Usually, several biopsies are obtained from the duodenum or jejunum because the disease process can be patchy. Biopsies also can be analyzed for disaccharidase enzyme activity. In addition, the procedure allows for provocative pancreatic secretion testing through the use of exogenous hormones, such as secretin or cholecystokinin, to measure pancreatic exocrine function.

Table 9. Second-phase Evaluation

- 72-hour quantitative fecal fat
- Breath hydrogen test
- Serum or urine D-xylose
- Vitamins A, D, E, and B12; prothrombin time; folate, zinc, iron, ferritin
- Radiolabeled Tc albumin lymphatic scan
- Endoscopy with biopsy for histology and disaccharidase analysis
- Pancreatic enzyme analysis

Summary

- Food is chemically reduced to digestive end products, made small enough to participate in the absorption process by various enzymes, and then transported across the intestinal epithelium by active transport, passive transport, facilitated diffusion, or endocytosis. Disruption of any of these physiologic stages may lead to maldigestion, malabsorption, or both.
- Based on strong research evidence, the most common type of carbohydrate malabsorption is lactose malabsorption due to "adult-onset" lactase deficiency. (1)
- Protein malabsorption leading to failure to thrive, hypoproteinemia, and edema occurs in pancreatic insufficiency, enterocyte deficiency, and impaired amino acid or peptide transport by the enterocyte.
- Fat malabsorption occurs in pancreatic insufficiency, which can be congenital in conditions such as cystic fibrosis and Shwachman-Diamond syndrome, or acquired, as in chronic pancreatitis. Fat malabsorption also is seen in diseases that impair bile production or excretion and in abetalipoproteinemia.
- A detailed history and physical examination and judicious use of laboratory studies usually provide the information necessary to diagnose a maldigestive or malabsorptive disorder.
- Management aims at enabling patients to grow and develop normally.

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PIR Quiz

Quiz also available online at pedsinreview.aappublications.org.

6. The primary pancreatic enzyme responsible for digesting starches in humans is:

   A. Amylase.
   B. Carboxypeptidase.
   C. Elastase.
   D. Lipase.
   E. Trypsin.

7. A 2-year-old child presents with a several-month history of chronic diarrhea, gas, and bloating. Endoscopy performed at age 20 months demonstrated a histologically normal bowel. On further questioning, you find that the family recently emigrated from Greenland. Of the following, the test that is *most* likely to identify the child's condition is:

   A. Fecal elastase.
   B. Repeat small bowel biopsy for enzyme analysis.
   C. Repeat small bowel biopsy for histology.
   D. Serum cholesterol.
   E. Sweat test.

8. Patients who have cystic fibrosis treated with high doses of pancreatic enzymes are at increased risk of developing:

   A. Cirrhosis.
   B. Diabetes mellitus.
   C. Emphysema.
   D. Fibrosing colonopathy.
   E. Gallstones.

9. An 18-month-old child presents to your practice with acute viral gastroenteritis. The *greatest* risk factor for the development of postinfectious diarrhea in this child is:

   A. Cow milk feeding during the illness.
   B. Family history of allergy.
   C. Gastroesophageal reflux.
   D. Immunodeficiency.
   E. Pre-existing malnutrition.

10. A 7-year-old patient who has had a Fontan procedure for hypoplastic left heart syndrome presents to your practice with chronic diarrhea. Of the following, which laboratory abnormality would suggest an intestinal protein-losing enteropathy?

   A. Elevated alanine aminotransferase.
   B. Hyponatremia.
   C. Hypothyroidism.
   D. Lymphopenia.
   E. Thrombocytopenia.

Malabsorptive Disorders of Childhood

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