Approach to the adult patient with suspected malabsorption

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INTRODUCTION

Intestinal malabsorption can arise from a wide variety of defects in luminal and brush border processing, absorption into the intestinal enterocyte, or the subsequent transport into the circulation [1]. Furthermore, one or more mechanisms may exist concurrently. Although chronic diarrhea (arbitrarily defined as that lasting >4 weeks) does not invariably accompany malabsorption, it is a frequent feature, so it warrants consideration of malabsorption as the underlying cause [2]. While the clinical presentation of patients with malabsorption may be similar, management is based on the underlying pathophysiology and may be quite different depending on the etiology. Thus, establishing a diagnosis of malabsorption is merely a first step; it is equally important to identify the underlying disease process causing the malabsorption.

This topic will review the clinical features and laboratory tools that can help establish a diagnosis of malabsorption. The pathophysiology and treatment of malabsorption and the approach to the adult with chronic diarrhea are discussed in detail separately. (See "Overview of nutrient absorption and etiopathogenesis of malabsorption" and "Overview of the treatment of malabsorption in adults" and "Approach to the adult with chronic diarrhea in resource-abundant settings".)

TERMINOLOGY

Definitions

- Maldigestion refers to impaired digestion of nutrients within the intestinal lumen (eg, exocrine pancreatic insufficiency) or at the terminal digestive site of the brush border membrane of mucosal epithelial cells (eg, lactose maldigestion).

- Malabsorption refers to impaired transport of nutrients across the apical membrane of enterocytes [3]. Defects in the steps that occur after absorption into the enterocyte (the processing phase) that impede the transfer of nutrients into the systemic circulation are rare (eg, intestinal lymphangiectasia and abetalipoproteinemia).

Although malabsorption and maldigestion are pathophysiologically distinct, the processes underlying digestion and absorption are interdependent, so that in clinical practice, the term malabsorption has come to denote derangements in either process. Unless otherwise specified, the term "malabsorption" in this topic refers to this more overarching meaning.

Classification — Malabsorption is not a single disease; rather, it is the consequence of many disease processes. There are different ways to categorize patients in terms of clinical severity and pathophysiology.

- **Global malabsorption** – Global malabsorption results from diseases associated with either widespread mucosal involvement or a reduced absorptive surface. Typically, a broad array of nutrients are not adequately absorbed. An example is celiac sprue, in which impaired absorption of almost all nutrients occurs.

- **Selective malabsorption** – Selective or isolated malabsorption results from diseases that interfere with the absorption of a single nutrient or a limited array of nutrients. An example is pernicious anemia, a disease that leads to defective cobalamin (vitamin B12) absorption.

- **Primary, or congenital malabsorption** – Malabsorption results from congenital defects in the membrane transport systems of the intestinal epithelium.

- **Acquired malabsorption** – Malabsorption results from acquired defects (eg, Crohn disease, celiac disease, or after extensive surgical resection or intestinal bypass operations) in the epithelial absorptive surface.

CLINICAL MANIFESTATIONS

Clinical presentation — The classic manifestations of malabsorption are chronic diarrhea with pale, greasy, voluminous, foul-smelling stools and unintentional weight loss despite adequate food intake. Steatorrheic stool may be loose or formed but are generally bulky. However, the full spectrum of these findings is relatively uncommon, even with widespread mucosal disease causing malabsorption (table 1). The majority of patients have relatively mild gastrointestinal symptoms. In some cases, anorexia, flatulence, abdominal distension and borborygmi may be the only complaints. Abdominal pain is unusual except in individuals where the underlying disease causing malabsorption are conditions such as Crohn disease, intestinal lymphoma, chronic pancreatitis, or intestinal pseudo-obstruction (table 2). (See "Clinical presentation and diagnosis of primary gastrointestinal lymphomas", section on 'Clinical features' and "Chronic intestinal pseudo-obstruction: Etiology, clinical manifestations, and diagnosis" and "Chronic intestinal pseudo-obstruction: Etiology, clinical manifestations, and diagnosis", section on 'Clinical manifestations' and "Clinical manifestations, diagnosis, and prognosis of Crohn disease in adults".)

Clinical manifestations related to a specific micronutrient deficiency can predominate in some patients (table 2 and table 3). As an example, iron deficiency anemia or metabolic bone disease may be the only clue to the presence of celiac disease [4]. (See "Epidemiology, pathogenesis, and clinical manifestations of celiac disease in adults", section on 'Metabolic bone disorders'.)

Various types of dermatitis can be a manifestation of a water-soluble vitamin, essential fatty acid, or zinc deficiency. Follicular hyperkeratosis (as well as night blindness and xerophthalmia) can be the result of vitamin A deficiency, and photosensitive pigmented dermatitis may reflect niacin deficiency. Peripheral neuropathies may occur due to thiamine or vitamin B12 deficiency, or both (or more rarely to vitamin E, copper or essential fatty acid deficiencies). (See "Overview of vitamin A", section on 'Clinical manifestations' and "Overview of water-soluble vitamins", section on 'Deficiency (pellagra)' and "Treatment of vitamin B12 and folate deficiencies".)

Progressive protein-calorie malnutrition may occasionally lead to severe enough hypoalbuminemia to produce edema, ascites, and/or pleural effusions. A clinically significant degree of protein-losing enteropathy is unusual in malabsorption but, when present, can contribute to hypoalbuminemia. (See "Protein-losing gastroenteropathy", section on 'Clinical features' and 'Other infrequently performed tests' below.)

Laboratory findings — Anemia is a common consequence of malabsorption and may result from protein-calorie malnutrition, or deficiencies of certain specific micronutrients such as iron, folate, vitamin B12 and, far less commonly, copper (table 3). Folate and iron deficiencies often arise due to malabsorption from diffuse mucosal lesions of the proximal small intestine and/or gastric surgery, while copper deficiency usually occurs as a delayed consequence of bariatric surgery or excessive zinc supplementation. Vitamin B12 malabsorption can result from small intestinal bacterial overgrowth, pernicious anemia, chronic atrophic gastritis, ileal resection, or extensive ileal disease. Proton pump inhibitors, histamine 2 receptor blockers, and metformin produce B12 malabsorption, and their long-term use can result in clinically significant deficiency [5]. (See "Diagnostic approach to anemia in adults" and "Causes and pathophysiology of vitamin B12 and folate deficiencies", section on 'Causes of vitamin B12 deficiency'.)

Fat malabsorption often results in fat-soluble vitamin deficiencies. In prolonged fat malabsorption, biochemical evidence of essential fatty acid deficiency may also ensue, manifested by an abnormal triene/tetraene ratio or sub-normal plasma concentrations of alpha linoleic acid and linolenic acid. However, clinical manifestations (eg, dry scaly dermatitis, poor wound healing and, in infants and children, diminished growth, decreased visual acuity, and peripheral neuropathy) are rare. Peripheral eosinophilia may be indicative of eosinophilic gastroenteritis. (See "Micronutrient deficiencies associated with malnutrition in children", section on 'Essential fatty acid deficiency' and "Eosinophilic gastrointestinal diseases", section on 'Laboratory findings'.)

States of global malabsorption of a substantial degree may produce diminished concentrations of serum calcium, magnesium, and zinc. In patients with fat malabsorption, both vitamin D malabsorption as well as excessive fecal loss of calcium and magnesium (because of binding of these cations to malabsorbed fatty acids in the intestinal lumen) contribute to these deficiencies.

Magnesium is unique among the minerals since it is primarily absorbed in the distal small intestine and colon. In patients who have lost substantial amounts of distal small gut and colon, magnesium depletion may arise even in the absence of fat malabsorption. (See "Overview of nutrient absorption and etiopathogenesis of malabsorption", section on 'Vitamins, minerals, and trace elements'.)

INITIAL EVALUATION

Malabsorption should be suspected in a patient with chronic diarrhea, and/or unexplained weight loss or otherwise unexplained nutrient deficiencies. The goal of the initial clinical evaluation in a patient with suspected malabsorption is the following:

- Confirm the presence of malabsorption
- Determine whether there is impaired malabsorption of multiple nutrients (global malabsorption) versus selective malabsorption of a single nutrient (see 'Classification' above)
- Determine the underlying etiology

The information gained from the initial evaluation, which includes a history and physical examination and routine laboratory tests, will help determine the underlying etiology. (See 'Additional evaluation to determine the underlying etiology' below.)

History and physical examination — The etiology and type of malabsorption can often be obtained from a history. The history should include the duration of the symptoms, character of the stool, timing in relation to meals or other exacerbating factors, and the presence of associated symptoms (eg, abdominal pain, bloating, distension), as well as underlying medical conditions. A description of stools as pale, greasy, or floating is highly subjective and often misleading, but a history of oil droplets in the toilet bowl ("like someone poured vegetable oil in the toilet") is far more specific to the presence of fat malabsorption. However, stools may nevertheless appear normal when laden with excess fat. In cases where the malabsorption of fat is the predominant malabsorptive defect, patients are less likely to complain of watery diarrhea, excess flatus, and bloating, whereas these symptoms are common when carbohydrate malabsorption predominates (eg, lactose malabsorption). Symptoms due to carbohydrate malabsorption typically occur within 90 minutes of carbohydrate ingestion.

The medical history should also include a history of chronic intestinal disease, intestinal resection, bariatric surgery or other surgical interventions or radiation treatments to the abdomen, risk factors for celiac disease (eg, type 1 diabetes mellitus, family history of celiac disease, ethnic background), and history of excessive alcohol consumption, acute/chronic pancreatitis, or pancreatic surgery. Recurrent peptic ulcer disease may be indicative of either a gastrinoma or mastocytosis, each of which can cause malabsorption (table 4). Malabsorption in patients with a gastrinoma is due to inactivation of pancreatic enzymes by large volumes of acidic gastric secretions, and in mastocytosis is presumed to be due to either gastric hypersecretion and/or infiltration of the intestinal mucosa with mast cells. (See "Epidemiology, pathogenesis, and clinical manifestations of celiac disease in adults", section on 'Epidemiology' and "Etiology of acute pancreatitis", section on 'Etiology' and "Zollinger-Ellison syndrome (gastrinoma): Clinical manifestations and diagnosis" and "Mastocytosis (cutaneous and

systemic) in adults: Epidemiology, pathogenesis, clinical manifestations, and diagnosis", section on 'Signs and symptoms'.)

Roux-en-Y gastric bypass bariatric surgery often produces a mild degree of fat and protein malabsorption, although usually not to a clinically significant degree. It is less commonly apparent with sleeve gastrectomy. More importantly, both types of bariatric surgery frequently result in clinically relevant malabsorption and deficiencies of iron, vitamin B12, vitamin D, and sometimes copper [6]. (See "Bariatric surgery: Postoperative nutritional management", section on 'Micronutrient deficiency, supplementation, and repletion'.)

Routine laboratory tests

Blood tests — Blood tests by themselves are never adequate for establishing a diagnosis of malabsorption but can provide supportive evidence. An initial screen for nutritional deficits should include a complete blood count, red cell folate and serum iron, total iron binding capacity, vitamin B12, calcium, magnesium, albumin, carotene, and 25-hydroxyvitamin D. Furthermore, decrements in serum concentrations of specific nutrients and vitamins may point towards the underlying cause and its duration (table 2). Fat-soluble vitamin levels may be altered due to changes in carrier proteins, which, like albumin, decrease in systemic inflammatory states. (See 'Approach' below.)

Stool tests for fat malabsorption — The malabsorption of fat is the most commonly used indicator of global malabsorption as it tends to be the most sensitive among the macronutrients (fat, carbohydrates, and protein) to interference from disease processes. In addition, since it is the most calorically dense macronutrient, its malabsorption is a critical factor in the weight loss that often accompanies malabsorptive disorders.

- **Fecal fat** – As a general rule, begin with a qualitative assessment of fecal fat on a single specimen since it is inexpensive and easy to perform for both the patient and the laboratory. When performed by an experienced laboratory, it is a valuable screening tool. If the diagnosis remains in doubt, proceed with a quantitative assessment of stool fat via a traditional biochemical assay on a 72-hour stool collection if the qualitative test is positive, or if it is negative but the clinical suspicion for malabsorption is high. Alternative and more convenient methods of quantitating excess fat in the stool, such as near-infrared reflectance analysis and the acid steatocrit, are accurate, but not yet widely available in the United States [7].

- **Sudan III stain** – The qualitative Sudan III stain, if properly performed on a spot sample of stool, has been variously reported to possess a sensitivity of 80 to 99 percent in detecting patients with clinically significant steatorrhea [8,9]. There is limited

evidence that assessing both the number of fat globules and their average size improved the accuracy of the assay while allowing for quantitative evaluation of the data [8]. Nevertheless, variability in the performance and interpretation of the test can limit its overall reliability, so it should be performed by an experienced and meticulous operator [9]. "Neutral" versus "split" fecal fat can be determined after the stool samples are stained with Sudan III before and after acidification and heating: neutral fat will be stained under basal conditions, and split fat will stain after acidification and heating. However, this has not been found to be a valid method of distinguishing maldigestion versus malabsorption [10].

- **72-hour fecal fat excretion** – The gold standard for the diagnosis of steatorrhea remains a biochemical quantitative assay for stool fat on a 72-hour stool collection. However, quantitative fecal fat determination does not discriminate between causes of steatorrhea. Accurate interpretation of the stool fecal fat depends on patient adherence to diet and proper collection. Patients should therefore be instructed to do the following:

  - Discontinue exogenous pancreatic supplements and nonabsorbable fat substitutes (eg, olestra) two days prior to, and during, the collection [11].

  - Consume 60 to 125 g per day of dietary fat for accurate determination (normal, older adults may have excessive stool fat if they ingest more than 140 g fat per day). The test is unlikely to be accurate if less than 60 grams of fat are consumed each day.

  - Maintain a record of all dietary intake beginning the day before, and for the duration of the stool collection to improve test interpretation.

  - Collect all stools over a 72-hour period. A 72-hour collection reduces errors and variability that may occur if a shorter collection period is used. It also allows the estimation of daily stool weight as a secondary measure of malabsorption.

  Average stool weights per day in the United States are 200 grams for female adults and 220 grams for males. Patients with steatorrhea almost always have stool weights in excess of these values. In adults consuming at least 60 g of fat daily during the test, a fecal fat excretion >7 g per day indicates fat malabsorption. However, a more precise means of quantitating the integrity of fat absorption is determining the "fractional fat excretion" (ie, average grams of stool fat excreted per day divided by the average grams of fat consumed per day). Calculating the fractional excretion is particularly helpful if the patient's average fat consumption during the test has been outside of the

range of 90 to 110 g per day. Basal fat excretion in normal individuals is 3 to 4 grams per day, which is one reason an accurate test cannot be performed if the patient consumes <60 grams of fat per day.

Thus, in adults consuming at least 60 g fat daily during the test, a fecal fat excretion >7 g per day, or more precisely, a fractional fat excretion >7 percent, indicates fat malabsorption. Patients with steatorrhea usually excrete more than 20 g per day. An intermediate fat excretion of 7.1 to 14 grams per day (or a fractional excretion of 7.1 to 14 percent) should be interpreted with caution since fat excretion can be moderately increased in diarrheal diseases even in the absence of fat malabsorption [12]. Causes of false negative tests include insufficient fat consumption during the test, an incomplete stool collection, or continued use of pancreatic supplements during the collection in the setting of pancreatic insufficiency. The use of nonabsorbable fat substitutes (eg, olestra) can lead to false-positive results [11].

- **Near infrared reflectance analysis** – A novel method, near infrared reflectance analysis (NIRA) is being increasingly used in Europe and is also available in some centers in the United States [13-15]. NIRA is equally accurate but less time-consuming than a 72-hour fecal fat collection, and allows for simultaneous measurement of fecal fat, nitrogen, and carbohydrates in a single sample.

- **Acid steatocrit** – The acid steatocrit (a gravimetric assay performed on a spot stool sample) may provide an accurate and simplified method for detecting steatorrhea on a spot stool specimen. A study evaluating this technique found a sensitivity of 100 percent, specificity of 95 percent and positive predictive value of 90 percent compared to a 72-hour fecal fat collection [16].

ADDITIONAL EVALUATION TO DETERMINE THE UNDERLYING ETIOLOGY

Approach — If the history suggests a particular cause of malabsorption, testing can be directed to confirm the diagnosis. However, in some cases, the cause of malabsorption may be clear based on initial history (ie, cystic fibrosis) and additional evaluation may not be necessary to determine the underlying etiology. In individuals with unexplained fat malabsorption, further laboratory tests are required to identify the underlying cause. The subsequent choice of testing (eg, imaging, endoscopy, and/or breath tests) is based on the initial history, physical examination, and the results of these laboratory studies. (See 'History and physical examination' above.)

Examples of our approach to testing based on the clinical scenario are as follows:

- In patients with positive celiac serologies, we perform an upper endoscopy with multiple mucosal biopsies of the 2nd and 3rd portions of the duodenum. (See "Diagnosis of celiac disease in adults", section on 'Endoscopy with small bowel biopsy'.)

- In individuals with a history of pancreatitis or excessive alcohol use or a low fecal elastase, we begin with imaging of the pancreas with magnetic resonance cholangiopancreatography (MRCP). If pancreatic imaging is negative, we perform an endoscopic ultrasound evaluation. If no etiology is identified, but the clinical suspicion of exocrine pancreatic insufficiency remains high, direct pancreas function testing with an endoscopic secretin stimulation test should be performed if available. Assessment for pancreatic exocrine insufficiency is discussed in detail separately. (See "Exocrine pancreatic insufficiency", section on 'Diagnosis'.)

- In individuals with known, predisposing causes for small intestinal bacterial overgrowth (eg, adhesions or strictures, small intestinal diverticulosis, blind intestinal loops), we perform a breath test for small intestinal bacterial overgrowth, remaining mindful of the limited accuracy of these tests. (See "Small intestinal bacterial overgrowth: Clinical manifestations and diagnosis", section on 'Carbohydrate breath test'.)

- In patients without an identifiable cause/risk factors, we usually proceed with an upper endoscopy and colonoscopy with multiple mucosal biopsies to rule out other causes (eg, Crohn disease). If endoscopic evaluation is unrevealing, we perform imaging of the small bowel with computed tomography (CT) or magnetic resonance (MR) enterography. In this setting a d-xylose test can help establish a diagnosis of malabsorption and distinguish mucosal disease from conditions that cause maldigestion. (See 'Other infrequently performed tests' below.)

Laboratory tests — To evaluate the etiology of malabsorption, we perform the following laboratory tests:

- Serologic testing for celiac disease (see "Diagnosis of celiac disease in adults", section on 'Serologic evaluation' and "Diagnosis of celiac disease in adults", section on 'Overview')

- Fecal elastase to exclude maldigestion due to pancreatic insufficiency (see "Exocrine pancreatic insufficiency")

Endoscopy with biopsy — Macroscopic features on endoscopy may suggest the presence of an underlying cause of malabsorption, although intestinal biopsies are usually required to confirm

the etiology. As examples, a cobblestone appearance of the duodenal mucosa is seen in Crohn disease, while reduced duodenal folds and scalloping of the mucosa may be evident in celiac disease. The unusual finding of multiple jejunal ulcers may indicate the presence of jejunoileitis, a gastrinoma, or infiltrative disease such as lymphoma [17]. (See "Clinical manifestations, diagnosis, and prognosis of Crohn disease in adults", section on 'Endoscopy' and "Epidemiology, pathogenesis, and clinical manifestations of celiac disease in adults", section on 'Gastrointestinal manifestations'.)

Imaging

Small bowel — An upper gastrointestinal series with small bowel follow-through, or a CT or MR enterography can provide important information about the gross morphology of the small intestine and can identify small bowel diverticula or other anatomic abnormalities associated with bacterial overgrowth. Contrast radiography can also identify mucosal diseases that are not easily accessible by endoscopy. MR enterography or CT with intravenous contrast carries with them the additional advantage of detecting abnormalities within the wall of the intestine, deep to the mucosa. Nevertheless, the radiologic findings in malabsorption are generally nonspecific and contrast studies are relatively insensitive and are often normal in patients with disease confined to the mucosa.

The role of wireless video capsule endoscopy in patients with malabsorption is very limited and should be considered only when other avenues to reveal the etiology of malabsorption fail. While it allows for visualization of the entire small bowel, it does not allow for mucosal biopsy and is associated with a risk of retention. Also, wireless capsule endoscopy should be avoided in patients with known or suspected small bowel strictures or severe hypomotility. In patients with suspected Crohn disease associated with malabsorption, small bowel imaging is required prior to capsule endoscopy. (See "Wireless video capsule endoscopy", section on 'Indications' and "Wireless video capsule endoscopy", section on 'Crohn disease'.)

Pancreas — Pancreatic imaging by CT or MRCP, may be helpful in the diagnosis of chronic pancreatitis and may be critical for distinguishing benign from malignant causes. Sequential dilation and sacculation of the pancreatic duct are pathognomonic of chronic pancreatitis (image 1). However, normal pancreatic imaging does not exclude the presence of pancreatic exocrine insufficiency. The secretin stimulation test remains the most sensitive means of diagnosing pancreatic insufficiency in centers in which it is performed accurately. The test involves intubation of the duodenum and the collection of pancreatic juices after intravenous secretin injection. Pancreas function testing and the secretin stimulation test are discussed in detail separately. (See "Exocrine pancreatic insufficiency", section on 'Direct pancreatic function tests' and "Chronic pancreatitis: Clinical manifestations and diagnosis in adults".)

Breath tests

Small intestinal bacterial overgrowth — The diagnosis of small intestinal bacterial overgrowth (SIBO) is supported by a positive glucose or lactulose breath test, or a positive jejunal aspirate culture; the latter being the gold standard. Breath tests are based on the principle that metabolism of a test dose of carbohydrate substrate by the bacterial flora leads to the production of an analyte (hydrogen, methane), which is absorbed and ultimately excreted in the breath. The accuracy of the breath tests in bacterial overgrowth are limited, nevertheless, most clinicians perform a carbohydrate breath test to diagnose SIBO as it is simple, non-invasive, and widely available. (See "Small intestinal bacterial overgrowth: Clinical manifestations and diagnosis", section on 'Diagnosis'.)

Malabsorption of specific carbohydrates — Breath tests are available to assess the integrity of lactose, fructose, and sucrose absorption. As a general rule, tests for detecting the malabsorption of a specific carbohydrate rely upon the fermentation of undigested carbohydrates by intestinal bacteria. Breath tests measure hydrogen, methane, or isotopically labelled $^{13}CO_2$ derived from sugars labelled with that stable isotope of carbon. The lactose breath test has been shown to be an accurate proxy measure of intestinal lactase content. However, insufficient data exists to define the accuracy of the fructose and sucrose tests. In the case of the fructose breath test, this is, in part, due to the fact that the entity of fructose intolerance remains a controversial diagnosis [18]. The sucrose breath test is typically used when there is a suspicion of a sucrase-isomaltase deficiency, an inborn error of metabolism; this entity is increasingly recognized as one that can masquerade as irritable bowel syndrome [19]. (See "Lactose intolerance and malabsorption: Clinical manifestations, diagnosis, and management", section on 'Malabsorption testing by hydrogen breath test'.)

Other infrequently performed tests

- **D-xylose absorption test for small bowel mucosal disease** – The D-xylose test measures the absorptive capacity of the proximal small intestine and is used to determine whether defects in the intestinal mucosa are responsible for malabsorption [20]. D-xylose is a pentose monosaccharide that can be absorbed both by an active sodium transporter and by passive diffusion. The dose used in testing is generally able to be absorbed by passive diffusion. Thus, the test is a measure of the permeability of the proximal small intestine, rather than a specific defect in D-xylose absorption. D-xylose absorption is normal in patients with intraluminal maldigestion caused by hepatobiliary disease or pancreatic insufficiency and in those with lymphatic obstruction. In contrast, D-xylose absorption is decreased in most patients whose malabsorption is due to mucosal disease (see 'Approach' above). Thus, it is useful in detecting the presence of malabsorption and

distinguishing it from maldigestion. Serial determinations of D-xylose absorption have also been reported to be a useful means of monitoring the efficacy of treatment of a malabsorptive disorder [21-23].

Following an overnight fast, the patient ingests a 25 g dose of D-xylose dissolved in water, and urine is collected for the next five hours. A venous blood sample is also collected after one hour. Normal excretion of D-xylose is 6.0 +/- 1.5 g (the lower limit of normal in individuals >65 is 3.5 g). Excretion of lesser amounts of D-xylose or a serum D-xylose concentration less than 20 mg/dL suggests abnormal absorption. Although less common, detecting the absorption of D-xylose has also been performed as a breath test and some investigators claim it is as accurate as the blood and urine determinations [21-23].

Although it remains a useful test, several conditions may lead to false-positive results. The presence of renal dysfunction or an inadequate urine sample is associated with falsely depressed urinary values of D-xylose although serum values should still be normal. The conventional D-xylose protocol is inaccurate for those older than 65 due to a decrease in the glomerular filtration rate associated with aging. False-positive results can also be seen with impaired gastric emptying, ascites, urinary retention, or fermentation of D-xylose by intestinal bacteria in patients with bacterial overgrowth. In addition, drugs such as neomycin, aspirin, indomethacin, and glipizide diminish urinary excretion of D-xylose.

- **Protein malabsorption** – Testing for protein malabsorption is rarely performed in the clinical setting and is reserved for patients with edema and hypoalbuminemia in whom there is no other apparent cause of protein loss (ie, proteinuria) or inadequate synthesis (ie, liver diseases) or supply (ie, protein malnutrition). Intestinal protein loss is more commonly a result of protein-losing gastroenteropathy, which can be demonstrated by measurement of the fecal alpha-1 antitrypsin. In massive enteral protein loss, the exact site of protein leakage may be localized by the infusion of 99mTc-albumin and gamma camera scintigraphy, however, the test is cumbersome and is infrequently performed. (See "Protein-losing gastroenteropathy", section on 'Diagnosis'.)

- **Bile acid malabsorption** – Malabsorption of bile acids with resulting diarrhea ("cholorrhea") is an entity distinct from the other types of malabsorption because it does not necessarily involve malabsorption of nutrients. Evaluation of bile acid absorption with a SeHCAT test can differentiate bile acid diarrhea from diarrhea due to fat malabsorption. The test involves the administration of a selenium^{75}-labeled synthetic bile acid (selen-homotaurocholic acid) orally, followed by measurement of retention of the radiolabeled bile acid by whole body scan or gamma camera at seven days (abnormal is less than 5 percent) [24,25]. However, SeHCAT is not available in many countries, including the United

States of America. Other tests of less proven accuracy include the measurement of a morning serum C4 (7a-hydroxy-4- cholesten-3-one), which is a direct measure of hepatic bile acid synthesis, and a 48-hour stool collection for total fecal bile acids [26].

In the absence of an objective test, patients with diarrhea due to cholorrhea can undergo a therapeutic trial with a bile acid-binding resin such as cholestyramine; resolution of symptoms supports the diagnosis of cholorrhea. In contrast, when bile acid malabsorption is severe enough to cause steatorrhea, cholestyramine can make the fat malabsorption worse, so instead, a fat-restricted diet should be pursued, with consideration of supplementation with medium chain triglycerides. Thus, distinguishing the two is important since management is different.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Acute diarrhea in adults" and "Society guideline links: Malabsorption".)

SUMMARY AND RECOMMENDATIONS

- Maldigestion refers to impaired digestion of nutrients within the intestinal lumen or at the terminal digestive site of the brush border membrane of mucosal epithelial cells. Malabsorption refers to impaired transport of nutrients across the apical membrane of enterocytes. Although malabsorption and maldigestion are pathophysiologically distinct, the processes underlying digestion and absorption are interdependent, so that in clinical practice, the term malabsorption has come to denote derangements in either process. (See 'Terminology' above.)

- The clinical presentation of malabsorption is highly variable, and is often far more subtle than the classical description of unintentional weight loss and overt steatorrhea (table 2). An important feature to establish early on in the evaluation of suspected malabsorption is determining whether impaired malabsorption of multiple nutrients is involved (global malabsorption) versus selective malabsorption of a single nutrient. Anemia is a common consequence of global malabsorption. In addition to the fecal loss of fatty acids, fat malabsorption often results in fat-soluble vitamin deficiencies. (See 'Clinical manifestations' above.)

- Malabsorption should be suspected in a patient with chronic diarrhea, and/or unexplained weight loss or otherwise unexplained nutrient deficiencies. Initial evaluation in patients with suspected malabsorption includes a history and physical examination and routine laboratory tests which include stool tests for malabsorption of fat and blood tests. Although a routine battery of blood tests (including some select fat- and water-soluble micronutrient assays) is helpful as an initial step when malabsorption is suspected, blood tests alone can only provide supportive evidence; they are never sufficient to establish a diagnosis of malabsorption. (See 'History and physical examination' above and 'Routine laboratory tests' above.)

- The underlying etiology of malabsorption can often be revealed by a detailed patient history. If the history suggests a particular cause, testing can be directed to confirm the diagnosis. Further testing may not be necessary in patients who have gross steatorrhea with an obvious cause (eg, cystic fibrosis or short bowel syndrome). In individuals with unexplained fat malabsorption, further testing will be required to establish the etiology, and the selection and order of tests should be based on the initial history, physical examination, and the results of initial laboratory studies. Thus, the order of testing and choice of particular tests should be individualized, and it is important to consider the availability and expertise needed for specialized testing. (See 'Initial evaluation' above and 'Additional evaluation to determine the underlying etiology' above.)

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Topic 4780 Version 27.0

GRAPHICS

Malabsorption: Conditions causing malabsorption, categorized by the phase of absorption that is impaired

Phase and nature of malabsorptive defect	Example
Luminal phase	
A. Substrate hydrolysis	
1. Digestive enzyme deficiency	Chronic pancreatitis
2. Digestive enzyme inactivation	Zollinger-Ellison syndrome
3. Dyssynchrony of enzyme release, inadequate mixing	Post Billroth II procedure
B. Fat solubilization	
1. Diminished bile salt synthesis	Cirrhosis
2. Impaired bile secretion	Chronic cholestasis
3. Bile salt de-conjugation	Bacterial overgrowth
4. Increased bile salt loss	Ileal disease or resection
C. Luminal availability of specific nutrients	
1. Diminished gastric acid	Atrophic gastritis - vitamin B12
2. Diminished intrinsic factor	Pernicious anemia - vitamin B12
3. Bacterial consumption of nutrients	Bacterial overgrowth - vitamin B12
Mucosal (absorptive) phase	
A. Brush border hydrolysis*	
1. Congenital disaccharidase defect	Sucrase-isomaltase deficiency
2. Acquired disaccharidase defect	Lactase deficiency
B. Epithelial transport	
1. Nutrient-specific defects in transport	Hartnup's disease
2. Global defects in transport	Celiac sprue
Postabsorptive, processing phase	
A. Enterocyte processing	Abetalipoproteinemia
B. Lymphatic	Intestinal lymphangiectasia

* This process is sometimes considered as part of the luminal phase.

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Graphic 54743 Version 5.0

Signs and symptoms of intestinal malabsorption

Malabsorption of	Clinical features	Laboratory findings
Calories	Weight loss with normal appetite	
Fat	Pale and voluminous stool, diarrhea without flatulence, steatorrhea	Fractional fat excretion (% of dietary fat not absorbed) >7%
Protein	Edema, muscle atrophy, amenorrhea	Hypoalbuminemia, hypoproteinemia
Carbohydrates	Watery diarrhea, flatulence, acidic stool pH, milk intolerance, stool osmotic gap	Increased breath hydrogen
Vitamin B12	Anemia, subacute combined degeneration of the spinal cord (early symptoms are paresthesias and ataxia associated with loss of vibration and position sense)	Macrocytic anemia, vitamin B12 decreased, serum methylmalonic acid and homocysteine increased
Folate (Vitamin B9)	Anemia	Macrocytic anemia, serum and RBC folate decreased, serum homocysteine increased
Vitamin B, general	Cheilosis, painless glossitis, acrodermatitis, angular stomatitis	
Iron	Microcytic anemia, glossitis, pagophagia	Serum iron, ferritin and iron saturation decreased
Calcium and vitamin D	Paresthesia, tetany, pathologic fractures due to osteomalacia, positive Chvostek and Trousseau signs	Hypocalcemia, serum alkaline phosphatase increased, abnormal bone densitometry
Vitamin A	Follicular hyperkeratosis, night blindness	Serum retinol decreased
Vitamin K	Hematoma, bleeding disorders	Serum vitamin K, vitamin K-dependent coagulation factors decreased

RBC: red blood cell.

Graphic 76166 Version 10.0

Laboratory features of global malabsorption

Decreased
Hemoglobin
Serum or RBC folate
Serum
Iron
Iron saturation
Ferritin
Vitamin B12
Calcium
Magnesium
Cholesterol
Carotene
Albumin
25-hydroxyvitamin D
Increased
Oxalate in urine
Prothrombin time

RBC: red blood count.

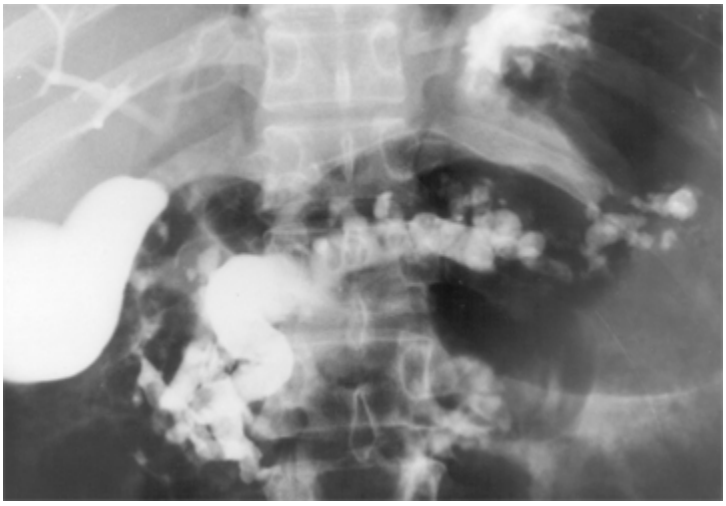
Graphic 53852 Version 3.0

Practical advice in the diagnosis of malabsorption

1. Stools may appear normal even when laden with excess fat.
2. Patients with carbohydrate malabsorption may have watery diarrhea and complain of excess flatus and abdominal distension. Symptoms typically occur within 90 minutes of carbohydrate ingestion.
3. Abdominal pain is unusual in malabsorption except in the case of selected diseases (eg, chronic pancreatitis, Crohn disease, or intestinal pseudo-obstruction).
4. Patients with celiac disease often have a childhood history of ill health and a positive family history of gluten sensitivity or Crohn disease. A subtle presentation, such as anemia or mildly elevated liver enzymes, is commonly the sole initial indication of disease.
5. The prevalence of celiac disease in patients with type 1 diabetes mellitus is higher than the general population.
6. Always ask about previous abdominal surgery.
7. Always ask about a history of recurrent peptic ulcer disease.
8. Do not forget to ask about alcohol consumption. It usually takes 10 to 20 years for pancreatic insufficiency to develop in alcoholics.

Graphic 59713 Version 4.0

ERCP in chronic pancreatitis



Severe pancreatic duct changes with dilation of the main pancreatic duct and of the primary and secondary branches.

ERCP: endoscopic retrograde cholangiopancreatography.

Graphic 62322 Version 6.0

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