Protein-losing gastroenteropathy

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INTRODUCTION

Protein-losing gastroenteropathies are characterized by an excessive loss of serum proteins into the gastrointestinal tract, resulting in hypoproteinemia, edema, and, in some cases, pleural and pericardial effusions. The diagnosis of protein-losing gastroenteropathy should be considered in patients with hypoproteinemia in whom other causes, such as malnutrition, heavy proteinuria, and impaired protein synthesis due to liver disease, have been excluded.

This topic will review the etiology, pathogenesis, clinical manifestations, diagnosis and management of protein-losing gastroenteropathy. Other causes of hypoalbuminemia are discussed elsewhere. (See "Overview of nutrient absorption and etiopathogenesis of malabsorption", section on 'Protein' and "Overview of heavy proteinuria and the nephrotic syndrome" and "Tests of the liver's biosynthetic capacity (eg, albumin, coagulation factors, prothrombin time)", section on 'Albumin'.)

PATHOGENESIS

The normal gastrointestinal tract does not contribute significantly to the catabolism of plasma proteins, accounting for only approximately 10 percent of the normal turnover of albumin and gamma globulin [1]. Once plasma proteins pass into the gastrointestinal tract, they are degraded rapidly to amino acids and reabsorbed into the portal circulation. The liver, as the primary site of plasma protein synthesis, can compensate for excess protein loss by increasing

production by up to 2.5 times its normal rate [2]. Protein-losing gastroenteropathy occurs when losses into the gastrointestinal tract exceed the liver's production capacity. This loss of serum proteins into the gastrointestinal tract occurs independent of molecular weight. Thus, the serum proteins most affected by this disrupted equilibrium are those with longer half-lives (ie, lower catabolic rate), like albumin, immunoglobulin A (IgA), IgG, IgM, ceruloplasmin, and fibrinogen. By contrast, there is little change in the serum concentrations of proteins with a rapid turnover rate (eg, transthyretin, insulin, IgE) [3].

In addition to proteins, other serum components that may also be lost in the gut include iron, lipids, and trace elements, many of which are protein-bound.

Intestinal leakage of plasma proteins occurs via one of the following mechanisms:

- **Inflammatory exudation** – Mucosal injury results in exudation of protein-rich fluids across the eroded epithelium. The degree of mucosal involvement typically correlates with the severity of protein loss.
- **Increased mucosal permeability** – Altered integrity of the mucosa of the stomach, small bowel, and colon due to inflammatory, infiltrative, and genetic causes results in protein leakage into the lumen.
- **Intestinal loss of lymphatic fluid** – Lymphatic obstruction, congenital abnormalities of the lymphatic system, or disorders of increased central venous pressure (eg, congestive heart failure or constrictive pericarditis) result in increased lymphatic pressure.

ETIOLOGY

Protein-losing gastroenteropathies can be caused by a diverse group of disorders (table 1).

Erosive gastrointestinal diseases — Enteral protein loss in patients with inflammatory bowel disease (eg, ulcerative colitis and Crohn disease) and gastrointestinal malignancies results from inflammatory exudation and absorptive loss from mucosal erosions and ulcerations. In addition, both Crohn disease and malignancy can cause lymphatic obstruction in the mesentery, leading to increased lymphatic pressure and the leakage of lymph into the gut lumen [4]. Protein-losing gastroenteropathy also occurs in a subset of patients with colitis due to *Clostridioides difficile* infection but not in patients with asymptomatic colonization [5,6]. (See "*Clostridioides difficile* infection in adults: Clinical manifestations and diagnosis".)

Nonerosive gastrointestinal diseases — A number of conditions, both congenital and acquired, can alter the integrity of the mucosa of the stomach, small bowel, or colon and cause

protein leakage into the lumen (table 1).

- **Intestinal disease** — Acquired protein-losing gastroenteropathy in celiac disease and tropical sprue is a consequence of the loss of villous structures and surface epithelium that facilitate the diffusion of plasma proteins between the cells. Other conditions that can be associated with protein-losing gastroenteropathy include allergic gastroenteropathy, eosinophilic gastroenteritis, collagenous colitis, systemic lupus erythematosus, and carbohydrate-deficient glycoprotein syndrome [7-11]. (See "Eosinophilic gastrointestinal diseases" and "Microscopic (lymphocytic and collagenous) colitis: Clinical manifestations, diagnosis, and management" and "Clinical manifestations and diagnosis of systemic lupus erythematosus in adults", section on 'Clinical manifestations'.)

  Congenital disorders of systemic immune regulation and cell membrane protein function can cause increased intestinal permeability or decreased luminal substrate absorption resulting in intestinal protein loss. Biallelic loss of function mutations in *CD55*, which encodes decay-accelerating factor and thereby regulates the complement cascade, has been associated with hyperactivation of complement, angiopathic thrombosis, and protein-losing enteropathy (CHAPLE syndrome) that results from membrane attack complex deposition and intestinal injury [12]. Additional rare genetic syndromes associated with gastrointestinal epithelial dysfunction include errors in lipid metabolism (mutations in *DGAT1* resulting in enterocyte toxicity [13,14]); aberrant intestinal protein deposition (mutation in *ANTRX2* causing intestinal hyalinosis [15]; and plasmalemma vesicle-associated protein deficiency (mutation in *PLVAP* [16]).

- **Giant hypertrophic gastropathy** — Several proliferative, inflammatory, and infiltrative conditions are associated with large or giant mucosal folds in the stomach and protein-losing gastroenteropathy. Of these, Ménétrier disease is the most common gastric disorder associated with gastrointestinal protein loss [17]. Increased intracellular permeability and wider tight junctions between cells leads to protein-rich exudates in the stomach. Other gastric causes of protein-losing gastroenteropathy include *Helicobacter pylori* gastritis and lymphocytic gastritis [12,18-21]. (See "Approach to the patient with large gastric folds", section on 'Ménétrier's disease' and "Approach to the patient with large gastric folds", section on 'Other causes'.)

- **Amyloidosis** — Patients with gastrointestinal amyloidosis can present with protein-losing gastroenteropathy due to mucosal infiltration [22]. (See "Gastrointestinal amyloidosis: Clinical manifestations, diagnosis, and management", section on 'Gastrointestinal tract amyloidosis'.)

Diseases with lymphatic obstruction/altered lymphatic flow — Intestinal lymphangiectasia is characterized by impaired small intestinal lymph drainage associated with dilated intestinal lymphatic channels. It can be due to primary malformation of intestinal lymphatics or secondary to other causes (eg, right-sided heart failure) (table 1).

- **Primary intestinal lymphangiectasia** — Primary intestinal lymphangiectasia is characterized by diffuse or localized ectasia of enteric lymphatics, often associated with lymphatic abnormalities elsewhere in the body [23]. The ectatic lymphatics may be located in the mucosa, submucosa, or subserosa. In patients with lymphatic obstruction and particularly congenital lymphangiectasia, loss of lymphocytes into the gut can produce significant lymphocytopenia with detectable alterations in cellular immunity.

  The disease primarily affects children and young adults. The mean age of onset is approximately 11 years, but patients often have symptoms much earlier [23]. Still, milder cases have been reported in older adults [24]. Although most cases are sporadic, primary intestinal lymphangiectasia has been reported in multiple siblings of several families, suggesting that, at least in certain cases, it may have an underlying genetic cause. Intestinal lymphangiectasia has also been reported in association with the yellow-nail syndrome (triad of pulmonary disease, lymphedema, and slow-growing, yellow nails without a cuticle or lunula), Turner, Noonan, Hennekam, von Recklinghausen, and Klippel-Trenaunay syndromes [16,25-29]. Several rare genetic syndromes have also been associated with protein-losing enteropathy. The pathogenesis in these cases is largely lymphatic obstruction leading to intestinal lymphangiectasia. The disorders include camptodactyly-arthropathy-coxa vara-pericarditis syndrome (mutations in *PRG4* [30]); protein-losing enteropathy with intestinal lymphangiectasia and skeletal dysplasia (mutations in *FGFR3* [31]); and tuberous sclerosis (mutation in *TSC2* [32]).

- **Secondary intestinal lymphangiectasia** — The most common causes of secondary intestinal lymphangiectasia are obstructive and include cardiac diseases and retroperitoneal lymph node enlargement due to malignancy or chemotherapeutic, infectious, or toxic substances (table 1) [33]. Cardiac conditions can lead to the development of secondary lymphangiectasia via an increase in central venous pressure, impeding drainage of the thoracic duct into the left subclavian vein. These include structural heart disease (eg, tricuspid insufficiency, congenital pulmonic stenosis, and atrial septal defect), constrictive pericarditis, cardiomyopathy, and single-ventricle physiology after surgical repair of complex congenital heart disease (eg, Fontan procedure) [34-38]. Secondary intestinal lymphangiectasia has also been described in patients with portal hypertension or hepatic venous outflow obstruction after liver

transplantation, and in congenital hepatic fibrosis due to phosphomannose isomerase deficiency [39] (see "Management of complications in patients with Fontan circulation", section on 'Protein-losing enteropathy'). Malignancies including lymphomas and neuroblastoma can directly obstruct lymphatic drainage and cause upstream lymphatic dilation [40,41].

CLINICAL FEATURES

Clinical manifestations — The clinical manifestations of protein-losing gastroenteropathy are highly variable and are determined by the underlying cause. Patients usually present with peripheral edema. Rarely, patients may present with gradually progressive dyspnea or painless abdominal distention due to symptomatic pleural effusions or ascites. Gastrointestinal symptoms of diarrhea, steatorrhea, abdominal pain, bloating, or flatulence may be present (table 1).

Patients with primary intestinal lymphangiectasia present in childhood with edema, weight loss, intermittent diarrhea, nausea, and vomiting. Some patients develop steatorrhea. Peripheral edema is often present and may be pitting if it results from hypoalbuminemia, or asymmetric and nonpitting if it results from an underlying lymphatic conduction abnormality affecting the extremity. Chylothorax or chylous ascites may also be present in patients with a systemic disease or widespread lymphatic malformation. (See "Pleural fluid analysis in adults with a pleural effusion" and "Etiology, clinical presentation, and diagnosis of chylothorax" and "Chylous, bloody, and pancreatic ascites", section on 'Chylous ascites'.)

Patients with protein-losing gastroenteropathy secondary to cardiac disease can have profound hypoproteinemia with clinically significant nutritional and immunologic consequences. Clinical features include edema, ascites, pleural and pericardial effusions, failure to thrive, frequent infections, and in some cases, sepsis due to chronic hypogammaglobulinemia. Severe third-spacing of body fluids further compromises the already tenuous hemodynamics and intravascular volume loss. The combination of increased central venous pressures and low cardiac output places the patient at risk for thromboembolism. (See "Management of complications in patients with Fontan circulation", section on 'Thrombosis' and "Management of complications in patients with Fontan circulation", section on 'Protein-losing enteropathy'.)

Hypogammaglobulinemia and lymphocytopenia in patients with protein-losing gastroenteropathy are variable. The consequences of these apparent quantitative immune defects are unclear; while case reports exist suggesting a correlation between hypogammaglobulinemia and an increase in opportunistic infections, this observation is

inconsistent [42]. Furthermore, diseases typically associated with lymphocytopenia have not been observed, even in patients with low CD4+ counts [43].

Laboratory findings — The main laboratory findings in PLE are reduced serum concentrations of albumin, gamma globulins (IgA, IgG, IgM), fibrinogen, cholesterol, transferrin, and ceruloplasmin (table 2). Deficiencies in minerals bound to albumin, ceruloplasmin, and other carrier proteins including zinc, copper, and iron may follow. Patients may have fat-soluble vitamin deficiencies.

DIAGNOSIS

Protein-losing gastroenteropathy should be suspected in patients with edema and hypoalbuminemia in whom there is no other apparent cause of protein loss (eg, proteinuria), inadequate synthesis (eg, liver diseases), or supply (eg, protein malnutrition). The diagnosis of protein-losing gastroenteropathy is established by an increase in alpha-1 antitrypsin clearance.

Alpha-1 antitrypsin is a glycoprotein synthesized in the liver and is the main component of the alpha-1 globulins. Alpha-1 antitrypsin has a higher molecular weight than albumin and is excreted intact in the stool because it is resistant to proteolysis and degradation in the intestinal lumen [44,45]. The normal rate of alpha-1 antitrypsin excretion in the stool is less than 2.6 mg/g stool which reflects an intestinal clearance of less than 13 mL/day [45,46]. Elevated alpha-1-antitrypsin clearance suggests increased enteral protein loss.

The alpha 1-antitrypsin clearance test requires a 24-hour stool specimen and a serum sample for simultaneous measurement of alpha 1-antitrypsin in plasma.

Alpha 1-antitrypsin clearance = (stool volume) x (stool alpha 1-antitrypsin)/ (serum alpha-1 antitrypsin)

Diarrhea, even in the absence of protein-losing gastroenteropathy, can increase clearance of alpha-1 antitrypsin from plasma [46]. Alpha-1 antitrypsin clearance values indicative of protein-losing enteropathy are greater than 27 mL/24 hours in patients without diarrhea and greater than 56 mL/day in patients with diarrhea.

Alpha-1 antitrypsin is degraded by gastric acid with a pH below 3.5. In patients with suspected hypertrophic secretory gastropathy or in those with apparent gastrointestinal protein loss but a normal alpha-1 antitrypsin clearance, alpha-1 antitrypsin clearance should be performed while the patient is on acid suppression (eg, omeprazole 40 mg once daily) [45,47].

Intestinal bleeding can significantly increase alpha-1 antitrypsin clearance rates [46].

Clearance of radiolabeled macromolecules (eg, 51Cr-labeled albumin, 125-I-labeled albumin, and 99mTc-labeled transferrin) is not routinely performed to diagnose protein-losing gastroenteropathy, as alpha-1 antitrypsin clearance is less expensive and less cumbersome to perform. The sensitivity and specificity of alpha-1 antitrypsin clearance as compared with 51Cr-labeled albumin are 93 and 90 percent, respectively [45].

Random fecal alpha 1-antitrypsin concentration is not a reliable test for protein-losing gastroenteropathy. There is poor correlation between random stool alpha-1 antitrypsin concentrations and alpha-1 antitrypsin clearance measurements [46].

DETERMINING THE ETIOLOGY

Our approach — In most patients, the etiology can be established from the history, physical examination, and laboratory data (table 1). The information gained from the initial evaluation will guide further testing. For example, patients with dyspnea on exertion should undergo echocardiography. (See 'Additional testing' below.)

If patients have symptoms suggesting either an upper or lower gastrointestinal etiology, it is reasonable to start the evaluation with an upper endoscopy or colonoscopy, respectively. If patients do not undergo both an upper endoscopy and colonoscopy initially and no lesion is identified during the initial examination that explains the protein-losing gastroenteropathy, the other test (either an upper endoscopy or colonoscopy) should be performed. If both upper endoscopy and colonoscopy are negative, abdominal imaging should be pursued.

For patients who are asymptomatic, we typically start with abdominal imaging to identify the underlying etiology. If the etiology is still not apparent, we perform endoscopic evaluation with both an upper endoscopy and colonoscopy.

We perform a video capsule endoscopy if the underlying etiology continues to remain uncertain.

History and physical examination — The history should include the duration of symptoms and the presence of associated symptoms (eg, onset of edema in the hands and feet of a newborn girl is suggestive of Turner syndrome; the presence of shortness of breath may be due to heart failure or pleural effusion).

A history of risk factors for protein-losing gastroenteropathy should be sought. This includes a history of recent travel to areas endemic for parasitic infections, recent antibiotic use that might predispose to an infection with *C. difficile,* chemotherapy, and NSAID exposure. Other important

historical features include a history of inflammatory bowel disease, rheumatic disease (eg, systemic lupus erythematosus), gastrointestinal malignancy, or heart disease (table 1).

Physical examination findings that may be suggestive of the underlying etiology include an elevated jugular venous pressure in a patient with right-sided heart failure. (See "Heart failure: Clinical manifestations and diagnosis in adults" and "Differentiating constrictive pericarditis and restrictive cardiomyopathy".)

Laboratory studies — Laboratory evaluation in patients with established protein-losing gastroenteropathy should include:

- Complete blood count with differential
- Serum chemistries including electrolytes and aminotransferases
- Celiac serologies if endoscopy has not already been performed

In addition, serum albumin, serum retinol, 25-hydroxyvitamin D, alpha-tocopherol, and prothrombin time should be obtained to assess the degree of hypoalbuminemia and to detect associated fat-soluble vitamin deficiencies. (See 'Laboratory findings' above.)

Laboratory studies should also include stool examinations for infectious etiologies:

- Ova and parasites
- Stool *C. difficile* toxin
- *Giardia* stool antigen test, particularly if the patient has risk factors such as recent travel to endemic areas

Imaging — Computed tomography scan or magnetic resonance imaging of the abdomen may demonstrate lymphadenopathy suggestive of lymphoma, mesenteric panniculitis suggestive of sclerosing mesenteritis, and thickening of the bowel wall suggestive of inflammatory bowel disease or infectious colitis. In patients with primary intestinal lymphangiectasia, mucosal folds appear thickened and nodular-simulating stacked coins [48]. (See "Clinical presentation and initial evaluation of non-Hodgkin lymphoma", section on 'Abdomen and pelvis' and "Sclerosing mesenteritis" and "Clinical manifestations, diagnosis, and prognosis of ulcerative colitis in adults", section on 'Imaging' and "Clinical manifestations, diagnosis, and prognosis of Crohn disease in adults", section on 'Imaging' and "*Clostridioides difficile* infection in adults: Clinical manifestations and diagnosis", section on 'Radiographic imaging'.)

Dynamic contrast magnetic resonance lymphangiography (DCMRL) is increasingly available. Using this technique, direct percutaneous lymphatic vessel access with targeted contrast injections can effectively map segments of the lymphatic system and localize specific lymphatic

abnormalities [49,50]. In some patients with protein-losing enteropathy (PLE), intrahepatic lymphatic duct contrast injection reveals direct communication between lymphatic vessels and the duodenal lumen [51]. Extravasation of contrast into the duodenal lumen confirms the PLE diagnosis and localizes the site of enteric protein leak.

In patients with intestinal lymphangiectasia, abnormal intestinal lymphatics can also be demonstrated by contrast lymphangiography and nuclear scintigraphy [52,53]. However, these tests are rarely performed and offer little additional information once an alpha-1 antitrypsin clearance test has been performed. Neither is particularly effective at localizing the site of enteric leak, and the value of these techniques in routine clinical practice is not established. Nuclear scintigraphy has been reported to demonstrate the abnormal intestinal lymphatics by using a technetium-labeled tracer (usually albumin or dextran) and assessing intestinal leakage [52,53].

Endoscopy and biopsy — Patients with hyperplastic gastropathies (eg, Ménétrier disease, hyperplastic hypersecretory gastropathy, and Zollinger-Ellison syndrome) have enlarged gastric folds or rugae on endoscopy. Patients with Zollinger-Ellison syndrome may have multiple peptic ulcers. (See "Approach to the patient with large gastric folds", section on 'Ménétrier's disease' and "Zollinger-Ellison syndrome (gastrinoma): Clinical manifestations and diagnosis", section on 'Endoscopic features'.)

In patients with primary intestinal lymphangiectasia, scattered white spots (snowflake-like appearance) overlie the small intestinal mucosa [54,55]. Consumption of a high-fat meal the evening before endoscopic evaluation can make these findings more apparent. Histopathologic examination reveals markedly dilated lymphatics that are most apparent in the tips of the villi. In addition, electron microscopy reveals dilated lymphatic vessels filled with chylomicrons and precipitated lymph proteins. These findings are also present in the dilated intraepithelial gaps extending from the basolateral membrane to the apical region of the epithelium.

> Endoscopic findings in patients with inflammatory bowel disease and microscopic colitis are nonspecific, and biopsies of the colon are necessary to establish the diagnosis and rule out other causes of colitis. Histopathological findings in patients with inflammatory bowel disease and microscopic colitis are discussed in detail separately. (See "Clinical manifestations, diagnosis, and prognosis of ulcerative colitis in adults", section on 'Endoscopy and biopsy' and "Clinical manifestations, diagnosis, and prognosis of Crohn disease in adults", section on 'Endoscopy' and "Microscopic (lymphocytic and collagenous) colitis: Clinical manifestations, diagnosis, and management", section on 'Endoscopy and biopsy'.)

Additional testing — Additional testing should be guided by the signs and symptoms and results of prior evaluation.

- **Autoantibody testing and related studies** – In patients with features in their medical history, physical examination, or other testing (eg, serum creatinine) that suggests a possible systemic rheumatic disorder, we obtain serologic and other studies based upon the specific condition suspected from the features that are present.
- **Echocardiogram** – In patients with clinical suspicion of cardiac involvement, such as signs or symptoms of heart failure, we obtain an echocardiogram.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of protein-losing gastroenteropathy is broad and varies based on the clinical presentation. The differential diagnosis of hypoalbuminemia and edema includes renal disease with proteinuria, liver diseases leading to inadequate protein synthesis, and protein malnutrition. (See "Pathophysiology and etiology of edema in adults" and "Overview of heavy proteinuria and the nephrotic syndrome".)

MANAGEMENT

Goals of therapy for patients with protein-losing gastroenteropathy include maximizing nutritional status and quality of life by reducing symptoms and sequela. Long-term management of protein-losing gastroenteropathy consists of two components:

- Dietary therapy to improve nutrition
- Treatment of the underlying disease when present

Serum protein levels (albumin, immunoglobulins, transferrin) should be monitored regularly, with the goal to bring these values as close to normal as possible. The percentage of patients in whom hypoalbuminemia can be corrected varies considerably and depends upon the type and severity of the underlying disease. In patients with severe erosive disease or intestinal dysmotility, when protein requirements can only be partially met by oral feeding and oral supplements, additional calories and protein can be delivered parenterally. At the same time, normal serum albumin concentrations are not necessary for symptom improvement or resolution, and the goal of care should be to safely maintain quality of life rather than prioritize normal serum protein concentrations. (See "Nutrition support in critically ill patients: An overview", section on 'Nutritional requirements'.)

Dietary therapy — The mainstay of dietary therapy is a low-fat, high-protein, high medium-chain triglyceride (MCT) diet. This approach is associated with favorable effects on hypoalbuminemia, gastrointestinal symptoms, and growth [48,56,57]. Patients should work closely with an experienced dietitian.

The diet in patients with protein-losing gastroenteropathy should be low in long-chain fatty acids, generally present as long-chain triglycerides (LCTs). The theoretical basis for a low LCT diet is that the reduction in intake of LCTs reduces lymphatic flow (driven by chylomicron export from intestinal epithelial cells into lacteals) and pressure in the lymphatic system, thus decreasing the quantity of enteric lymph leakage. There is no "one size fits all" diet, and different patients will likely tolerate different thresholds of LCT intake. Adjustments over time are usually necessary to find the appropriate balance between dietary restriction, symptom management, and quality of life.

In our practice, we start by limiting LCT intake to <10 percent of total calories. This typically translates to 10 to 20 g/day in children 1 to 10 years of age, and 15 to 25 g/day in people >10 years of age. Fat intake should be spread throughout the day, divided among meals and snacks, to minimize lymphatic flow from fat boluses. While reduction in LCT intake may decrease enteric protein loss, such a severe calorie restriction increases the risk of malnutrition and micronutrient deficiencies.

Calories lost from LCT restriction can be replaced with MCTs, which include saturated fatty acids of 6 to 12 carbon atoms. As opposed to LCTs, MCTs are not re-esterified in the intestinal epithelial cells and are exported directly to the portal circulation rather than the lymphatic circulation. Various preparations of MCTs are commercially available as purified natural or synthetic oil, a modular powder, or as part of an oil blend. Some natural oils contain high percentages of MCT relative to LCT, including palm kernel and coconut oils; however, the LCT content in these oils may exceed tolerable levels. Excessive intake of MCTs can cause gastrointestinal distress, including nausea and diarrhea, so starting at a low dose and titrating up to a tolerable provision is advised. We typically start at 0.5 g/kg/day in children and 50 g/day in adults, divided into two to three doses over the day to minimize adverse effects. These doses can be titrated up to 1 to 1.5 g/kg/day and 100 g/day, respectively, based on patient tolerance.

In addition to making up the calorie deficit from an LCT-restricted diet, adequate essential fatty acids must be provided. Alpha-linolenic acid and linoleic acid are the essential long-chain polyunsaturated fatty acids [58]. While absolute requirements of alpha-linolenic acid and linoleic acid are minimal, 4 and 1 percent of overall calories, respectively, they are not commercially available individually and must be obtained from natural oils [59]. These are available in highest concentrations in flax seeds, walnuts, salmon, sardines, and soybeans, as well as in corn,

canola, and safflower oils. In patients who cannot tolerate enteral supplementation, topical applications have been attempted to prevent and treat essential fatty acid deficiency with mixed results [60-62]. However, this approach should be used as a last resort, to be considered in light of the patient's overall clinical status and deficiency risk.

Patients with PLE are at risk of fat-soluble vitamin deficiency from enteric loss of carrier proteins. In addition, fat-soluble vitamins require emulsification with bile salts and LCTs at the mucosal surface for efficient absorption into the enterocyte. Patients with PLE often require large doses of fat-soluble vitamin supplementation to overcome the poor absorption efficiency. When possible, these vitamins should be supplemented in water-miscible or water-soluble forms, and serum concentrations should be monitored every three to six months. Additional trace element and mineral supplementation may be required to achieve normal serum concentrations, particularly iron, zinc, and copper.

Protein requirements are increased in patients with PLE to 3 g/kg in children and adolescents and 1.5 to 3 g/kg/day in adults [63,64]. The diet can be supplemented by commercially available protein formulas. Isolated protein supplements (eg, Casec, ProMod, BeneProtein) are a reliable source of fat-free dietary protein, but are expensive and may be unpalatable. Supplements that provide both protein and nonprotein calories (eg, Ensure, Isocal, Peptamen, and PediaSure) may be more palatable. Whey protein supplements can be added to skim milk or starchy foods to increase protein intake.

For the infant with PLE, a number of formulas are commercially available that have MCT as the primary fat source (including Enfaport, Monogen). For older children and adults, available formulas are either fat-free (ProViMin, Tolerex, Vivonex T.E.N.) or low fat/high MCT (Lipistart, Portagen, Vivonex Pediatric). Most of these formulas are poorly tolerated due to taste and can be expensive. As not all of these formulas are otherwise nutritionally complete, their use should be supervised by an experienced dietitian.

Treatment of the underlying disease — Treatment of the underlying disease has been associated with regression of PLE. As examples, immunosuppressive therapy in patients with inflammatory diseases (eg, systemic lupus erythematosus, inflammatory bowel disease, gut graft versus host disease), pericardiectomy in patients with constrictive pericarditis, and repair of cardiac abnormalities and hepatic venous outflow obstruction [8,65-70]. The treatments used for specific disorders are described in detail separately. (See "Constrictive pericarditis: Management and prognosis", section on 'Treatment of late (chronic) disease'.)

Surgery (eg, intestinal resection or anastomosis of abnormal lymphatics to venous channels) should be reserved for patients with localized and refractory intestinal disease [48,71]. However,

these approaches are not always feasible.

The somatostatin analogue, octreotide, has been associated with an improvement in protein-losing gastroenteropathy in case reports of patients with Menetrier disease (100 micrograms twice daily) and primary intestinal lymphangiectasia (200 micrograms twice daily) [72,73]. However, there is insufficient evidence to routinely support its use. The mechanism by which octreotide decreases PLE is unclear but likely relates to the reduction in splanchnic blood flow, and thus reduced lymphatic pressure in the capillary bed.

In a case report, three patients in a family with CHAPLE syndrome were treated with eculizumab, a humanized monoclonal antibody to C5 [74]. Within 100 days of initiation of therapy there was a significant reduction in complement activation, an increase in serum albumin and total protein concentrations, and an improvement in diarrhea. While these data suggest the importance of complement activation in a subset of patients with PLE, the role of complement blockade in the treatment of protein-losing gastroenteropathy is unclear. (See 'Diseases with lymphatic obstruction/altered lymphatic flow' above.)

SUMMARY AND RECOMMENDATIONS

- Protein-losing gastroenteropathies are characterized by an excessive loss of serum proteins into the gastrointestinal tract. Protein-losing gastroenteropathies can be caused by a diverse group of disorders (table 1). (See 'Etiology' above.)
- Intestinal leakage of plasma proteins results from inflammatory exudation due to mucosal injury; increased mucosal permeability due to altered integrity of the mucosa of the stomach, small bowel, and colon; and increased lymphatic pressure in the gut. (See 'Pathogenesis' above.)
- The clinical manifestations of protein-losing gastroenteropathy are highly variable and are determined in part by the underlying cause (table 2). Patients usually present with peripheral edema. Rarely patients may present with gradually progressive dyspnea or painless abdominal distention due to symptomatic pleural effusions or ascites. Gastrointestinal symptoms of diarrhea, steatorrhea, abdominal pain, bloating, or flatulence may be present in patients with underlying small bowel or colonic disease. (See 'Clinical manifestations' above.)
- The main laboratory findings in protein-losing enteropathy are reduced serum concentrations of albumin, gamma globulins (IgA, IgG, IgM), fibrinogen, cholesterol,

transferrin, and ceruloplasmin. Patients may have fat-soluble vitamin deficiencies due to their underlying small bowel disease. (See 'Laboratory findings' above.)

- Protein-losing gastroenteropathy should be suspected in patients with edema and hypoalbuminemia in whom there is no other apparent cause of protein loss (eg, proteinuria), inadequate synthesis (eg, liver diseases), or supply (eg, protein malnutrition). The diagnosis of protein-losing gastroenteropathy is established by an increase in alpha-1 antitrypsin clearance. (See 'Diagnosis' above.)

- Once the diagnosis of protein-losing gastroenteropathy is established, the underlying etiology should be determined. In most patients, the diagnosis can be established from the history, physical examination, and laboratory data. The information gained from the initial evaluation will guide further testing. (See 'Determining the etiology' above and 'Our approach' above.)

- Management of protein-losing gastroenteropathy consists of dietary therapy to improve nutrition and treatment of the underlying disease. The mainstay of dietary therapy is a low-fat, high-protein, medium-chain triglyceride diet. (See 'Management' above.)

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GRAPHICS

Causes of protein-losing gastroenteropathy

Inflammatory exudation due to mucosal erosions or ulcerations
Inflammatory bowel disease
Crohn disease
Ulcerative colitis
Gastrointestinal malignancy
Gastric cancer
Lymphoma
Kaposi sarcoma
Alpha chain disease
Pseudomembranous colitis due to *Clostridium difficile*
Erosive gastritis and multiple gastric ulcers
Nonsteroidal antiinflammatory drug (NSAID) enteropathy
Post-chemotherapy
Cap polyposis
Graft-versus-host disease
Intestinal loss of lymphatic fluid due to lymphatic obstruction
Primary intestinal lymphangiectasia
Right-sided heart failure
Heart failure
Constrictive pericarditis
Congenital heart diseases
Fontan procedure for single ventricle
Retroperitoneal lymph node enlargement (eg, due to chemotherapy, infection, or toxin exposure)
Cirrhosis/portal hypertensive gastropathy

Increased permeability due to mucosal disease without erosions or ulcerations
Celiac disease
Tropical sprue
Giant hypertrophic gastritis (Ménétrier's disease)
Possible relation to *Helicobacter pylori* infection
Lymphocytic gastritis
Secretory hypertrophic gastropathy
Amyloidosis
Infections
Bacterial overgrowth
Acute viral infection
Parasitic infection
Whipple disease
Rheumatic diseases
Systemic lupus erythematosus
Rheumatoid arthritis
Mixed connective tissue disease
Intestinal vasculitis
Allergic gastroenteropathy
Eosinophilic gastroenteritis
Collagenous colitis
Congenital disorders of glycosylation
Congenital enterocyte heparin sulfate deficiency

Hepatic venous outflow obstruction
Enteric-lymphatic fistula
Mesenteric venous thrombosis
Mesenteric tuberculosis or sarcoidosis
Sclerosing mesenteritis
Neoplasia involving the mesenteric lymph nodes or lymphatics
Chronic pancreatitis with pseudocysts
Crohn disease
Whipple disease
Thoracic duct obstruction
Congenital malformations of lymphatics
Retroperitoneal fibrosis

Graphic 53419 Version 9.0

Clinical manifestations and laboratory abnormalities in patients with protein-losing gastroenteropathy

Clinical manifestations
Edema
Ascites
Pleural effusion
Pericardial effusion
Laboratory abnormalities
Hypoalbuminemia without proteinuria, disorders associated with decreased protein synthesis, or malnutrition
Reduced plasma concentrations of:
Gamma globulins
Cholesterol
Alpha-1 antitrypsin
Fibrinogen
Ceruloplasmin
Lymphopenia
Malabsorption of fat and fat-soluble vitamins

Graphic 65661 Version 3.0

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