REVIEW ARTICLE

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Protein-Losing Enteropathy

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Protein-losing enteropathy is an uncompensated loss of plasma proteins in the intestine, indicated by elevated alpha$_1$-antitrypsin levels in the stool, which leads to panhypoproteinemia in the absence of liver or kidney disease. Protein-losing enteropathy is a syndrome, not a disease; therefore, it is important to identify the underlying cause.[1] Many acquired and congenital diseases are manifested as protein-losing enteropathy (Tables 1 and 2). Generally, these disorders either damage the intestinal mucosa or block gastrointestinal lymphatic flow through obstruction and lymphangiectasia. Improved diagnostic approaches, especially genomic testing, have revealed disease entities causing protein-losing enteropathy and have led to the development of effective therapies.

The presenting features of protein-losing enteropathy are hypoproteinemia, edema, nutritional deficiencies, infections, and gastrointestinal symptoms, including diarrhea, steatorrhea, abdominal pain, and vomiting. Hypoproteinemia is nonselective, with reduced albumin and immunoglobulin levels. Edema (of the face and arms and legs) and effusions (peritoneal, pleural, and pericardial) are caused by reduced oncotic pressure in blood. Infections can result from hypogammaglobulinemia and lymphopenia. In children, malabsorption and malnutrition may be severe, resulting in retarded growth and development.

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PHYSIOLOGY

Blood contains well-defined proteins that are normally maintained at specific concentrations.[1] Serum albumin, at 35 to 55 g per liter (approximately 0.6 mM), provides 80% of the oncotic pressure, serves molecular transport, maintains serum pH, and carries out antioxidant and esterase reactions. Albumin is secreted by hepatocytes through fenestrated sinusoidal capillaries at a rate of 10 to 15 g per day (Fig. 1),[63] with a turnover rate of 5% per day (half-life, 15 days).[64] Hypoalbuminemia can be "sensed" by the liver, and albumin production can be increased, but this process cannot fully compensate for gastrointestinal albumin loss in patients with protein-losing enteropathy.[64]

The second most abundant serum protein class is immunoglobulins, at 7.5 to 22 g per liter (Fig. 1).[65] Although circulating immunoglobulins can normally exit the vasculature, especially during infections, this process is accelerated in protein-losing enteropathy into the gut lumen.[66] In addition, other, less abundant proteins, including acute-phase reactants, have reduced concentrations in patients with protein-losing enteropathy.[67]

Since protein-losing enteropathy is manifested as nonselective depletion of all plasma proteins, selective protein deficiencies indicate conditions other than protein-losing enteropathy. For example, hypoalbuminemia with normal immunoglobulin levels may reflect liver disease, reduced low-molecular-weight proteins indicate the nephrotic syndrome or other kidney diseases, and low immunoglobulin levels suggest immunodeficiency.

Table 1. Epidemiologic and Clinical Characteristics of Acquired Protein-Losing Enteropathy (PLE) Disorders and Specific Management Options.*

Condition	Frequency of PLE	Relative Effect of PLE	Treatment and Outcome	Study
Systemic inflammatory disorders				
Crohn's disease	Excessive GI protein loss occurs in most patients	Clinically significant PLE is rare relative to the high frequency of GI protein loss; loss of immunoglobulins can occur	Glucocorticoids and medications for IBD usually reverse PLE	Samant et al.,[4] Karback and Ewe[5]
Ulcerative colitis	Frequency is unknown	Clinically significant PLE is rare	PLE may respond to antiinflammatory treatment or surgery	Ungaro et al.[6]
SLE	Frequency is approximately 3%	PLE may precede full-blown SLE; inflammatory manifestations of SLE affecting other organ systems usually correlate with occurrence of PLE	PLE usually responds to glucocorticoids (alone or in combination with immunosuppressive agents)	Al-Mogairen,[7] Pachas et al.,[8] Mok et al.[9]
Other inflammatory disorders†	PLE is a common manifestation of GVHD affecting the GI tract; data for other conditions are scarce	PLE may cause severe symptoms, but its overall effect is variable	PLE may respond to glucocorticoids or immunosuppressive agents; in glucocorticoid-resistant gut GVHD, infusion of human-derived alpha$_1$-antitrypsin may be effective	Nakamura et al.,[10] Ishige et al.,[11] Rao et al.,[12] Weisdorf et al.,[13] Shulman et al.,[14] Giannoni et al.[15]
Giant hypertrophic gastropathy (Ménétrier's disease)	Excessive GI protein loss occurs in approximately 85% of patients, with peripheral edema due to hypoalbuminemia in approximately 38%	The classical triad comprises GI symptoms, peripheral edema, and giant gastric folds	Cetuximab or gastrectomy may be considered in refractory cases	Lambrecht[16]
Food protein–induced gut disorders				
Food allergy (mainly, eosinophilic gastroenteritis)	An estimated 20% of patients have PLE	Edema may be a predominant manifestation	Glucocorticoids and avoidance of food antigens may reverse PLE	Waldmann et al.,[17] Chehade et al.,[18] Mikhail and Sampson[19]
Celiac disease	Most untreated patients have excessive GI protein loss	PLE has a minor effect	PLE responds to gluten-free diet	Bai et al.[20]
Cardiovascular disorders				
Constrictive pericarditis	PLE is rare	PLE causes variable edema and GI symptoms	Pericardiectomy can reverse PLE	Wilkinson et al.,[21] Bauer et al.[22]
Heart conditions with chronically elevated systemic venous pressures‡	PLE occurs in up to 18% of patients undergoing the Fontan procedure	PLE is mild to very severe, even lethal	PLE responds to dietary modification and pharmacotherapy (e.g., diuretics, glucocorticoids, octreotide)	Johnson et al., [23] Moodie et al.,[24] Mertens et al.,[25] Gleason et al.[26]
Long-standing congestive heart failure	PLE is infrequent	PLE usually has a minor effect	PLE responds to treatment of heart failure	Davidson et al.,[27] Berkowitz and Segal[28]

Neoplasms				
General cancers	PLE frequency depends on the type of cancer but is usually low	PLE may be an initial manifestation or occasionally precedes cancer by a prolonged period	Cancer chemotherapy may lead to reversal of PLE in some cancers	
Carcinoma of the esophagus, stomach, or bowel				Waldmann et al.[29]
Kaposi's sarcoma (often associated with AIDS and organ transplantation)				
Lymphoma				Cashen et al.[30]
Neuroblastoma				Citak et al.[31]
Multiple myeloma				Bhat et al.[32]
Waldenström's macroglobulinemia				Cooke et al.[33]
Langerhans' cell histiocytosis				Santos-Machado et al.[34]
Lynch syndrome				
Abnormal proliferative lesions, polyps, and vascular malformations				
Abnormal proliferative lesions	PLE is rare	Effect of PLE depends on the organs involved	Specific treatment may reverse PLE (e.g., sirolimus in lymphangioleiomyoma); resection of polyps can reverse PLE in patients with familial polyposis	
Lymphangioleiomyomatosis (sporadic or associated with tuberous sclerosis complex)				Nishino et al.,[35] Pollack et al.[36]
Lymphangiomatosis				Lin et al.[37]
Neurofibroma or vascular changes due to neurofibromatosis				Tatemichi et al.[38]
Infantile systemic hyalinosis due to *ANTXR2* mutations				Alreheili et al.[39]
Familial polyposis due to SMAD4 defects				Johansson et al.[40]

Table 1. (Continued.)

Condition	Frequency of PLE	Relative Effect of PLE	Treatment and Outcome	Study
Infections and infestations				
Tropheryma whipplei	Hypoalbuminemia and intestinal manifestations are common; histopathological assessment reveals lymphangiectasia in many patients	PLE has a variable effect; GI manifestations or other systemic features may be more prominent	Antibiotics, alone or in combination with glucocorticoids, often reverse PLE	Arnold et al.[41]
Opportunistic infections, generally associated with AIDS§	PLE frequency was higher in AIDS before HAART but is now greatly reduced	PLE may be prominent, but its effect depends on the use of HAART and accompanying manifestations	PLE responds to HAART and specific treatment of the pathogen (e.g., antimycobacterial therapy for *Mycobacterium avium* complex)	Laine et al.,[42] Ogawa et al.,[43] Perrineau et al.[44]
Enteric infections¶	Many infections can involve PLE, but pathogen-specific frequency is unknown	Effect of PLE depends on the type of infection; occasionally, edema due to hypoproteinemia is predominant	PLE responds to specific antimicrobial therapy (e.g., metronidazole for giardiasis)	Sullivan et al.,[45] Akkelle et al.,[46] Su et al.[47]

* The list of conditions is adapted from Strober and Fuss,[1] Brownell and Piccoli,[2] and Greenwald.[3] AIDS denotes acquired immunodeficiency syndrome, GI gastrointestinal, GVHD graft-versus-host disease, HAART highly active antiretroviral therapy, IBD inflammatory bowel disease, and SLE systemic lupus erythematosus.
† Other inflammatory disorders include Henoch–Schönlein purpura, Sjögren's syndrome, pemphigus vulgaris, rheumatoid arthritis (in association with secondary amyloidosis), tropical sprue, radiation enteritis, GVHD, necrotizing enterocolitis, and sarcoidosis.
‡ Chronically elevated systemic venous pressures can develop after the Fontan or Glenn procedure or as a result of baffle obstruction after the Mustard operation has been performed for transposition of the great arteries.
§ Opportunistic pathogens include *M. avium* complex, cytomegalovirus, cryptosporidia, and cystoisospora.
¶ Enteric pathogens include *Strongyloides stercoralis*, giardia, bacterial overgrowth in the small intestine, salmonella, shigella, campylobacter, *Clostridium difficile*, and *Helicobacter pylori*.

Protein-losing enteropathy also involves the wasting of all other interstitial fluid components.[1-3] The pressure of each heart beat drives fluid containing albumin, immunoglobulins, and other serum components from peripheral blood vessels into the interstitium (Fig. 1). Inflammation increases capillary permeability and interstitial influx. Interstitial fluid is recirculated by the lymphatics, which are tributaries to the arteriovenous circulation that start as open-ended vessels in the interstitium. Lymphatics have valves for one-way flow down a shallow pressure gradient to the thoracic duct, which returns to the subclavian vein. Lymph flow is screened for pathogenic agents through lymph nodes (Fig. 1). Foodstuffs, nutrients, and micronutrients, such as calcium, magnesium, zinc, iron, and copper, are absorbed in the gut interstitium of the villus, which contains a central intestinal lymphatic or lacteal (Fig. 2A).[2,68] Other blood constituents, including hematopoietic cells, fats, and vitamins, also enter the lymph. Epithelial cells connected by tight junctions guard the integrity and composition of the gut interstitium. Protein-losing enteropathy occurs when the intestinal epithelium is breached and the interstitial fluid leaks into the gut lumen.

PATHOPHYSIOLOGY AND DISEASE TAXONOMY

The two principal pathophysiological mechanisms that compromise epithelial retention of interstitial contents are direct mucosal damage (either erosive or nonerosive) and failed lymph drainage, causing backflow through the epithelium into the lumen (Fig. 2). Some diseases involve other pathophysiological mechanisms in addition to or instead of these two mechanisms. Comprehensive lists of diseases with protein-losing enteropathy have been published elsewhere.[1-3]

MUCOSAL DISEASES

Mucosal erosion occurs in inflammatory bowel disease, peptic ulcer, infections, and carcinoma (Fig. 2A and Table 1). Mucosal diseases cause loss of plasma proteins into the gut lumen. This is commonly seen in Crohn's disease, ulcerative colitis, erosive gastritis, the Zollinger–Ellison syndrome, and pseudomembranous colitides.[4] Other inflammatory conditions with erosive protein-losing enteropathy include sarcoidosis, graft-ver-

sus-host disease, and gastrointestinal amyloidosis. Infections can also precipitate inflammatory mucosal damage. Less commonly, epithelial tumors of the esophagus, stomach, and intestine and metastatic cancers lead to mucosal damage and protein-losing enteropathy. In rare cases, protein-losing enteropathy has occurred in patients with the acquired immunodeficiency syndrome (AIDS) who have Kaposi's sarcoma and in recipients of organ transplants.[69]

Nonerosive mucosal epithelial permeability occurs with inflammation, infection, allergic reactions, or a genetic abnormality affecting the mucosa. Local vasculitis or inflammatory cytokine secretion can aggravate protein-losing enteropathy by increasing interstitial fluid accumulation.[7,70] Protein-losing enteropathy can occur in systemic lupus erythematosus, Sjögren's syndrome, Henoch–Schönlein purpura, and pemphigus vulgaris.[7,8,10,11] Patients who have systemic lupus erythematosus with severe protein-losing enteropathy, called lupus protein-losing enteropathy, may present with edema, ascites, and pleural and pericardial effusions, together with abdominal pain, nausea, vomiting, and diarrhea.[7] Protein loss is seen in Ménétrier's disease, a usually nonerosive hypertrophic gastropathy involving overgrowth of mucus-secreting cells, decreased gastric acid secretion, dramatic mucosal fold thickening, and sometimes gastric cancer.[1,3] The juvenile polyposis syndrome may be manifested as protein-losing enteropathy, which can be reversed by polyp resection, and hemorrhagic hereditary telangiectasia.[40]

Allergic disorders, including eosinophilic gastroenteritis, may cause protein-losing enteropathy, and food elimination diets can reverse the process.[17-19] Celiac disease, an immune-mediated disorder triggered by a food antigen — specifically, gluten found in wheat and related prolamins from rye and barley — is frequently associated with protein-losing enteropathy, which correlates with the degree of villous architecture abnormality and responds to a gluten-free diet. Occasionally, severe edema is the presenting feature of celiac disease.

Diseases involving failure of the epithelial barrier also allow loss of interstitial fluid proteins into the intestinal contents. Heparan sulfate proteoglycans, located on the basolateral surface of intestinal epithelial cells, maintain tight intercellular junctions.[71] Molecular alterations in heparan sulfate, syndecans, or other surface proteins disrupt the gut barrier.[3] Protein-losing enteropathy can occur when intestinal epithelial cells lack heparan sulfate.[72]

DISEASES OF LYMPHATIC RETURN

Intestinal lymphatics were first identified by Gaspare Aselli, who described them in fed dogs as prominent white cords filled with chylous lymph in the mesentery. His findings were published in 1627 in his anatomical masterpiece, *De lactibus sive lacteis venis*.[73] Diseases that block lymphatic drainage cause pathological distention, distortion, and disruption of lymphatics, a condition that is called intestinal lymphangiectasia. In intestinal lymphangiectasia, lymph proteins are massively lost into the lumen, causing severe protein-losing enteropathy, whereas mucosal disorders are generally milder and more amenable to treatment. Intestinal lymphangiectasia is classified as primary if the defects are intrinsic to the lymphatic system and as secondary if external obstructions to lymph vessels or cardiovascular disease impair lymphatic flow (Fig. 2B). Engorged lacteals leak lymphatic fluid into the bowel lumen, depleting proteins, lipids, and lymphocytes from the lymph and ultimately from the blood circulation. Intestinal lymphangiectasia leads to panhypoproteinemia and low blood levels of other nutrients and can be accompanied by lymphopenia, mainly involving naive CD4+CD45RA+ T cells.

Lymph recirculation requires intact vasculature with a pressure gradient guiding unidirectional flow to the right side of the heart. Heart conditions causing chronically elevated central venous pressure impede lymph return from intestinal lymphatics (Fig. 2B).[68] Constrictive pericarditis, long-standing congestive heart failure, or specific surgical interventions, such as the Fontan procedure, can cause secondary intestinal lymphangiectasia (Table 1 and Fig. 2B).[21,23-25,27] The Fontan procedure diverts venous blood directly to the pulmonary artery, which increases venous pressure on the right side of the heart, and protein-losing enteropathy develops in up to 18% of patients who undergo this procedure.[23,25] Surgical diversion of blood from the innominate vein to the atrium can relieve intestinal lymphangiectasia.[74] Similarly, pericardiectomy reverses intestinal lymphangiectasia and protein-losing enteropathy in patients with constrictive pericarditis.[21,22]

Table 2. Molecularly Characterized Hereditary PLE Disorders.*

Disorder	Gene	Inheritance	Comments	Clinical Features	Study
HKLLS1	*CCBE1*	AR	CCBE1 promotes VEGFC activation and lymphangiogenesis	Lymphedema in the arms and legs, lymphangiectasia, unusual facies, intellectual disability, short stature, microcephaly, cardiac malformations	Alders et al.[48]
HKLLS2	*FAT4*	AR	FAT4 regulates lymphatic-vessel morphogenesis	Overlap with HKLLS1	Alders et al.[49]
HKLLS3	*ADAMTS3*	AR	ADAMTS3 binds *CCBE1* for VEGFC activation to control lymphangiogenesis	Overlap with HKLLS1	Brouillard et al.[50]
Lymphatic malformation 6	*PIEZO1*	AR	PIEZO1 promotes blood and lymph-vessel development	Nonimmune hydrops fetalis, lymphedema, chylothorax, pericardial effusions	Fotiou et al.[51]
Noonan syndrome 1	*PTPN11*	AD	Tyrosine phosphatase is a ubiquitous protein	Lymphedema, lymphangiectasia, antenatal hydrops, short stature, learning difficulties, congenital heart disease, cryptorchidism, hernias, bleeding diathesis	Wang et al.[52]
Thanatophoric dysplasia, type I	*FGFR3*	AD	FGFR3, a receptor for fibroblast growth factors, is essential for bone formation	Growth retardation, facial features, thoracic and skeletal anomalies, with severe shortening of the limbs, macrocephaly, frontal bossing, prominent eyes, intellectual disability	Yang and Dehner[53]
Oculoskeletodental syndrome	*PIK3C2A*	AR	PIK3C2A, a member of the phosphoinositide 3-kinase family, functions in cell proliferation, survival, and migration	Congenital cataract, PLE due to IL, short stature and various skeletal anomalies, dysmorphic facial features and dental anomalies, developmental delay, stroke, hearing loss, secondary glaucoma, nephrocalcinosis	Tiosano et al.[54]
CHAPLE disease	*CD55*	AR	CD55 is a membrane inhibitor of the C3- and C5-convertase enzymes; C5- inhibitory antibodies reverse PLE and other manifestations	PLE due to IL; hypoalbuminemia causing edema, ascites, pericardial and pleural effusions; hypogammaglobulinemia; diarrhea, abdominal pain, and bowel inflammation causing ulcers and obstruction; thrombosis	Ozen et al.[55]

CDG	—	—	PMM2, MPI, ALG6, ALG8, and ALG1 play a role in asparagine (N)–linked glycosylation†	—	—
Type Ia	*PMM2*	AR	—	Psychomotor retardation with generalized hypotonia, hyporeflexia, ataxia, and growth retardation; eye, arm and leg, and genital anomalies; lipodystrophy	Damen et al.[56]
Type Ib	*MPI*	AR	—	Liver disease, PLE, and hyperinsulinemic hypoglycemia (classical triad); coagulation abnormalities may be observed (thrombophilia and depletion of antithrombin, proteins C and S, factor XI)	Niehues et al.[57]
Type Ic	*ALG6*	AR	—	Feeding problems, neurologic problems (psychomotor retardation, hypotonia, epilepsy), strabismus, PLE, liver involvement, coagulation factor abnormalities	Westphal et al.[58]
Type Ih	*ALG8*	AR	—	Dysmorphism (retrognathia, low-set ears, talipes equinovarus), muscular hypotonia, hepatomegaly, coagulopathy, edema and ascites (including fetal hydrops), PLE	Chantret et al.[59]
Type Ik	*ALG1*	AR	—	Neurodevelopmental problems (developmental delay, hypotonia, epilepsy, microcephaly, intellectual disability), ocular abnormalities, facial dysmorphism, hematologic abnormalities, PLE	Ng et al.[60]
Diarrhea 10, PLE type	*PLVAP*	AR	PLVAP protein helps form fenestral diaphragms in blood vessels and lymphatic capillaries; loss of endothelial barrier leads to PLE	Intractable secretory diarrhea and massive protein loss due to leaky fenestrated capillaries, severe hypoalbuminemia, hypogammaglobulinemia, electrolyte deficiencies, hypertriglyceridemia; some patients have facial dysmorphism, cardiac and renal anomalies, hypothyroidism, venous thrombosis, iris abnormality	Elkadri et al.[61]
Diarrhea 7, PLE type	*DGAT1*	AR	DGAT1 enzyme functions in glycerophospholipid biosynthesis and triglyceride metabolism	Early-onset PLE, chronic diarrhea, malnutrition, hypoalbuminemia, lymphopenia, watery diarrhea, vomiting, abdominal pain	Haas et al.[62]

* AD denotes autosomal dominant, AR autosomal recessive, CDG congenital disorder of glycosylation, CHAPLE CD55 deficiency with hyperactivation of complement, angiopathic thrombosis, and protein-losing enteropathy, HKLLS Hennekam lymphangiectasia–lymphedema syndrome, IL intestinal lymphangiectasia, and VEGFC vascular endothelial growth factor C.
† Suggested mechanisms include intestinal lymphangiectasia or enterocyte dysfunction due to the reduction of glycoproteins (e.g., heparin sulfate). In type Ib, supplementation with a simple sugar, D-mannose, is effective in reversing PLE.

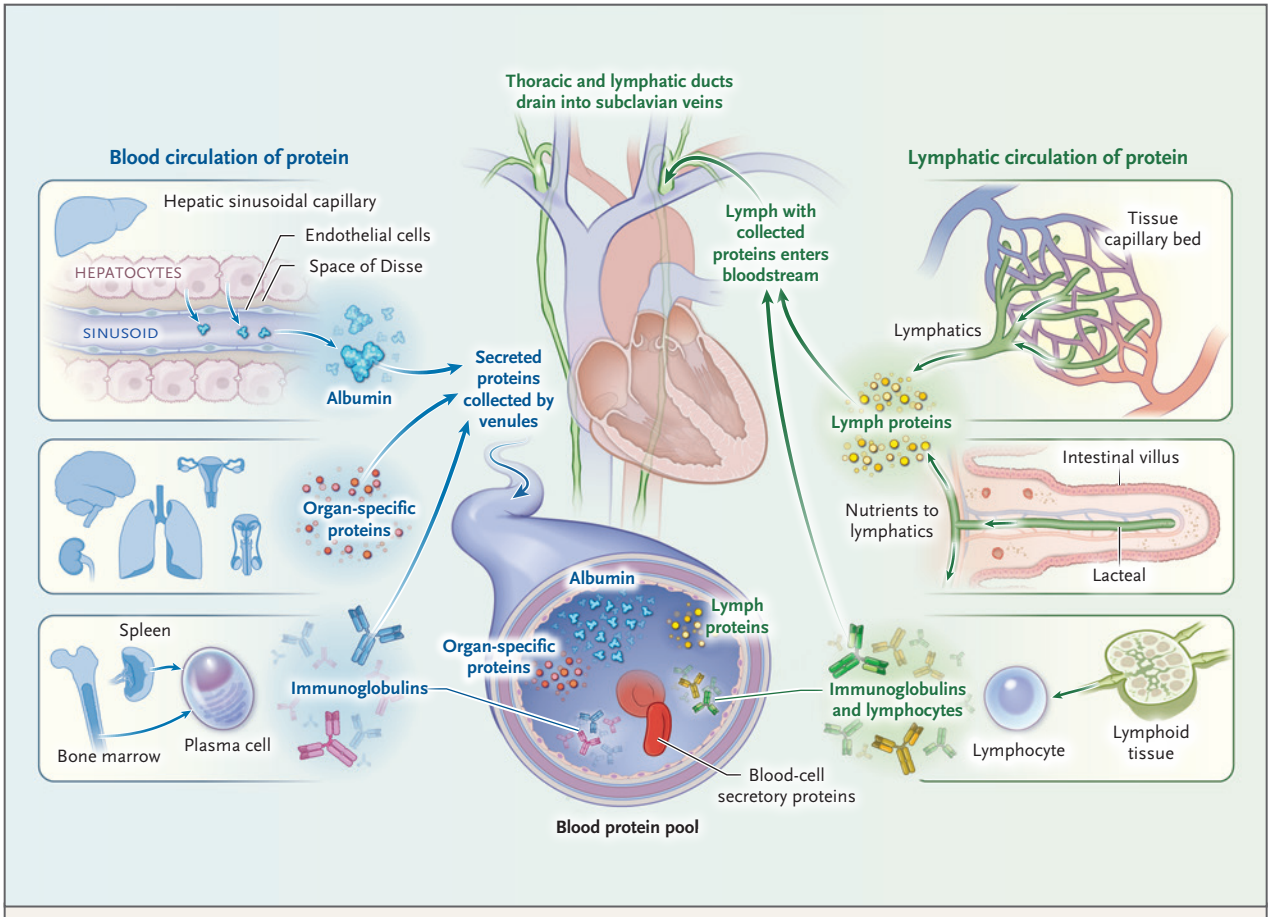

Figure 1. Protein Circulation in Blood and Lymph.

The major sources and circulation of protein between the blood and the lymphatic system are shown. The primary functions of the lymphatic circulation are to absorb the interstitial contents, especially fluid and proteins; transport fatty acids and nutrients from the intestinal villi; and add lymphocytes and immune mediators from the lymphoid tissues to the lymph fluid. The lymphatic ducts return lymph to the bloodstream (green arrows) as part of venous return on the right side (blue arrows). Thus, the blood protein pool is a mixture of the proteins transported by the veins and the lymphatics draining the tissues. Each organ contributes to the plasma protein composition; albumin and immunoglobulins are most abundant. Albumin, synthesized by the liver, equilibrates with venous blood in the space of Disse through the hepatic sinusoidal capillaries. Plasma cells, a type of differentiated B lymphocytes originating from the bone marrow, spleen, and lymphoid tissues, are the main source of circulating immunoglobulins.

Widespread or metastatic abdominal cancers can block lymph drainage, causing protein-losing enteropathy (Fig. 2B).[29] Examples include lymphoma, neuroblastoma, multiple myeloma, Waldenström's macroglobulinemia, Langerhans' cell histiocytosis, benign lymphatic tumors, and lymphangiomatosis.[31-37] Malignant lymphoma can retard flow through the retroperitoneal or mesenteric lymph nodes.[30] Chemotherapy-induced remission of lymphoma can reverse protein-losing enteropathy.[30,75] Protein-losing enteropathy may be the presenting or only manifestation of an early-stage neoplasm.

Nonmalignant cell proliferation may also cause protein-losing enteropathy. Tuberous sclerosis complex is a rare multisystemic disease due to mutations in *TSC1* or *TSC2* (tuberous sclerosis complex subunit 1 or 2), which cause widespread noncancerous cell growth that, if abdominal, may compress draining lymphatics. Lymphangioleiomyomatosis (LAM) associated with tuberous sclerosis complex, also called TSC-LAM, and sporadic LAM, which is independent of tuberous sclerosis complex, have been linked to intestinal lymphangiectasia. Sirolimus can reduce lymphangioleiomyomas and protein-losing enteropathy in

both patients with TSC-LAM and those with sporadic LAM.[35,36] These patients may have an inflammatory bowel disease–like intestinal inflammation, which can be ameliorated with sirolimus therapy. Infantile systemic hyalinosis due to mutations in *ANTRX2* (anthrax toxin receptor 2) is characterized by hyaline deposition in many tissues. In the gastrointestinal tract, this can lead to an obstructive protein-losing enteropathy.[39]

Protein-losing enteropathy can be both a cause and a consequence of thrombotic disease. It promotes thrombosis in diseases such as systemic lupus erythematosus with or without the antiphospholipid syndrome; Crohn's disease; ulcerative colitis; Waldenström's macroglobulinemia; CHAPLE disease (CD55 deficiency with hyperactivation of complement, angiopathic thrombosis, and protein-losing enteropathy), a lethal disease caused by the genetic loss of the complement regulatory protein CD55 (discussed below); glycosylation disorders; and a deficiency of *PLVAP* (plasmalemma vesicle–associated protein).[76] Pathologic mechanisms include loss of the inhibitory coagulation factors through gut wasting or overproduction of the prothrombotic factor fibrinogen in the liver. Protein-losing enteropathy may also be a consequence of blood clots that lodge in the gut, especially in the mesenteric veins and superior vena cava, which occur in primary thrombophilic conditions.[3,77]

Lymphatic damage or inflammation leading to intestinal lymphangiectasia can result from infection with bacteria, viruses, fungi, or parasites. Well-characterized agents are mycobacterium species and *Tropheryma whipplei* (the causative agent in Whipple's disease), but other, poorly defined infections can cause similar processes (Table 1).[78] Whipple's disease is a rare systemic chronic infection usually characterized by chronic diarrhea, hypoproteinemia, abdominal pain, malnutrition, and weight loss due to protein-losing enteropathy, as well as migratory polyarthralgia and enlarged lymph nodes. Protein-losing enteropathy is commonly due to enteric protein exudation, but active infection may phenocopy the hereditary lymphedema syndrome.[41,78] Intestinal lymphangiectasia and protein-losing enteropathy are due to characteristic macrophages containing bacilli and lipid deposits that infiltrate lymph vessels. AIDS can cause protein-losing enteropathy due to opportunistic infections, neoplasms, and ulcerative colitis of unknown cause.[42] The pathogens that cause enteric infections in patients with AIDS include cryptosporidia, cystoisospora, cytomegalovirus, and *Mycobacterium avium* complex, which may obstruct mesenteric and retroperitoneal lymphatics and cause protein-losing enteropathy.[43,79,80] When the causative agent is known, protein-losing enteropathy can generally be managed by means of targeted therapy with specific antimicrobial agents.

CONGENITAL CAUSES OF PROTEIN-LOSING ENTEROPATHY

Congenital protein-losing enteropathy disorders can be defined by specific gene mutations that provide molecular and mechanistic information about pathophysiological features and by potential treatment options (Table 2). These new insights have led to the development of a molecular taxonomy that complements the clinicopathological analysis and facilitates precision diagnostics and treatments (Table 2). Thus, clinically similar protein-losing enteropathy conditions can be managed with treatments that differ according to the specific molecular pathogenesis.

Primary intestinal lymphangiectasia involving peripheral lymphatic malformations is increasingly defined by genetic defects that involve endothelial, connective-tissue, immune, and metabolic abnormalities (Table 2). Faulty lymph-vessel development links protein-losing enteropathy and intestinal lymphangiectasia to primary lymphedema disorders in the Hennekam lymphangiectasia–lymphedema syndrome (HKLLS). In HKLLS, generalized lymphatic dysplasia affects multiple organs and is accompanied by facial dysmorphism and cognitive impairment (Table 2). Deleterious mutations in three genes — *CCBE1* (collagen and calcium–binding EGF domains 1), *FAT4* (FAT atypical cadherin 4), and *ADAMTS3* (ADAM metallopeptidase with thrombospondin type 1 motif 3) — can cause HKLLS types 1, 2, and 3, respectively.[48-50] Other primary causes of intestinal lymphangiectasia include the lymphatic malformation 6 syndrome, which is associated with damaging mutations in *PIEZO1* (piezo type mechanosensitive ion channel component 1), and the Noonan syndrome, caused by mutations in *PTPN11* (protein tyrosine phosphatase nonreceptor type 11).[51,52] These syndromes occur early in 32 termed lymphedema, as opposed to the symmetric pitting edema usually observed with protein-losing enteropathy.[1] Thanatophoric dysplasia,

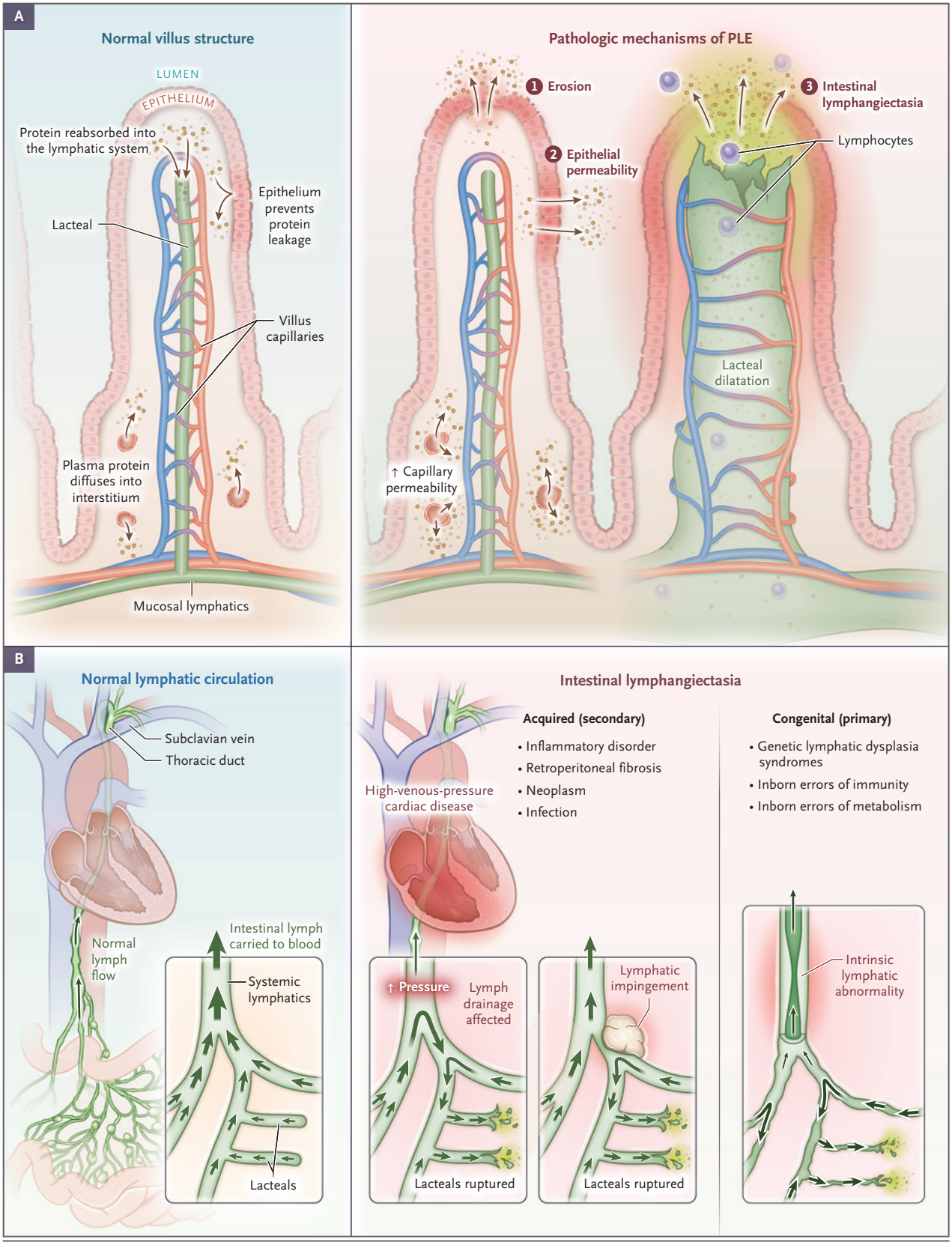

Figure 2 (facing page). Mechanisms of Enteric Protein Loss in Different Classes of Protein-Losing Enteropathy (PLE) Disorders.

The structure of the normal intestinal villus and the pathologic mechanisms causing protein loss are shown in Panel A. Circulating proteins and cells egress from the capillaries to the interstitium and are collected by the lymph vessels, including lacteals, and transported back to the blood. PLE disorders can involve one or more of the three mechanisms shown, with the rate-limiting step for protein loss differing in each condition: capillary diffusion of proteins into the interstitium in diseases with erosion, epithelial permeability in nonerosive intestinal disorders, and leakage and rupture of dilated lacteals in intestinal lymphangiectasia. Also, increased capillary permeability can lead to interstitial fluid accumulation and can aggravate PLE. Intestinal lymphatic circulation in the healthy state and in different classes of intestinal lymphangiectasia is shown in Panel B. Each disorder affects the circulatory network differently, but all the disorders have an effect on the anterograde flow in the distal channels. Eventually, the flow is reversed, causing dilatation and rupture of the lacteals and thereby decompressing the system at the expense of lymph wasting. The width and orientation of the arrows show the speed and direction of the lymph, respectively.

caused by mutations in *FGFR3* (fibroblast growth factor receptor 3), and the oculoskeletodental syndrome, caused by mutations in *PIK3C2A* (phosphatidylinositol-4-phosphate 3-kinase catalytic subunit type 2 alpha), may be accompanied by protein-losing enteropathy due to intestinal lymphangiectasia.[53,54]

CHAPLE disease, a newly characterized primary intestinal lymphangiectasia, results from inherited *CD55* mutations. CD55 is a cell-surface regulator of the C3 complement convertase, and genetic loss of the CD55 protein causes complement-mediated damage and blockade of the lymphatic vessels and intestinal lymphangiectasia.[55,81] Severe protein-losing enteropathy and thrombosis can lead to failure to thrive and early death. Discovery of the molecular pathogenesis suggested the use of complement inhibitory therapeutics, and clinical trials now show that this approach is effective in reducing or reversing all the manifestations of the disease.[81] Thus, an understanding of the molecular pathogenesis of a severe primary intestinal lymphangiectasia has led to a highly effective intervention.

In type I congenital disorders of glycosylation, intestinal lymphangiectasia or enterocyte dysfunction due to the reduction of surface glycoproteins such as heparan sulfate can result in protein-losing enteropathy.[58,82] Genetic defects in asparagine (N)–linked glycosylation of proteins have broad pathologic effects that are due to defective function of proteins lacking appropriate glycan side chains.[83] Five genes have been linked to protein-losing enteropathy in type 1 congenital disorders of glycosylation: *PMM2* (phosphomannomutase 2) in type Ia, *MPI* (mannose phosphate isomerase) in type Ib, *ALG6* in type Ic, *ALG8* in type Ih, and *ALG1* in type Ik (Table 2).[56-60] Each congenital disorder of glycosylation has unique clinical features in addition to protein-losing enteropathy, and coagulation abnormalities are common. At present, it is not known which specific proteins, when abnormally glycosylated, account for the protein-losing enteropathy. Type Ib (MPI-associated) congenital disorder of glycosylation can be treated with D-mannose administration.[83]

PLVAP is expressed in endothelial cells and functions as part of a physical barrier between blood and the interstitium.[61] A deficiency of *PLVAP* disrupts endothelial fenestral diaphragms in the intestinal vasculature and causes protein-losing enteropathy, hypertriglyceridemia, and venous thrombosis (Table 2).[61]

Other genetic deficiencies affect diverse pathways, leading to distinct mechanisms of gut protein wasting (Table 2). *DGAT1* (diacylglycerol O-acyltransferase 1) is highly expressed in the small intestine and catalyzes the final step in triglyceride synthesis. *DGAT1* deficiency is a rare recessive disease that leads to severe, often lethal protein-losing enteropathy,[62] which may be due to the buildup of lipid substrates in the epithelium, underscoring the importance of lipid regulation for intestinal integrity.

DIAGNOSIS

Protein-losing enteropathy is diagnosed by ruling out other causes of hypoproteinemia and diarrhea or malabsorption; documenting enteric protein loss; performing imaging studies of the cardiovascular, thoracic, and abdominopelvic structures; assessing systemic manifestations of protein-losing enteropathy; and carrying out histopathological and, possibly, genetic testing (Fig. 3, and Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Hypoproteinemia is the most frequent manifestation of protein-losing enteropathy. Therefore,

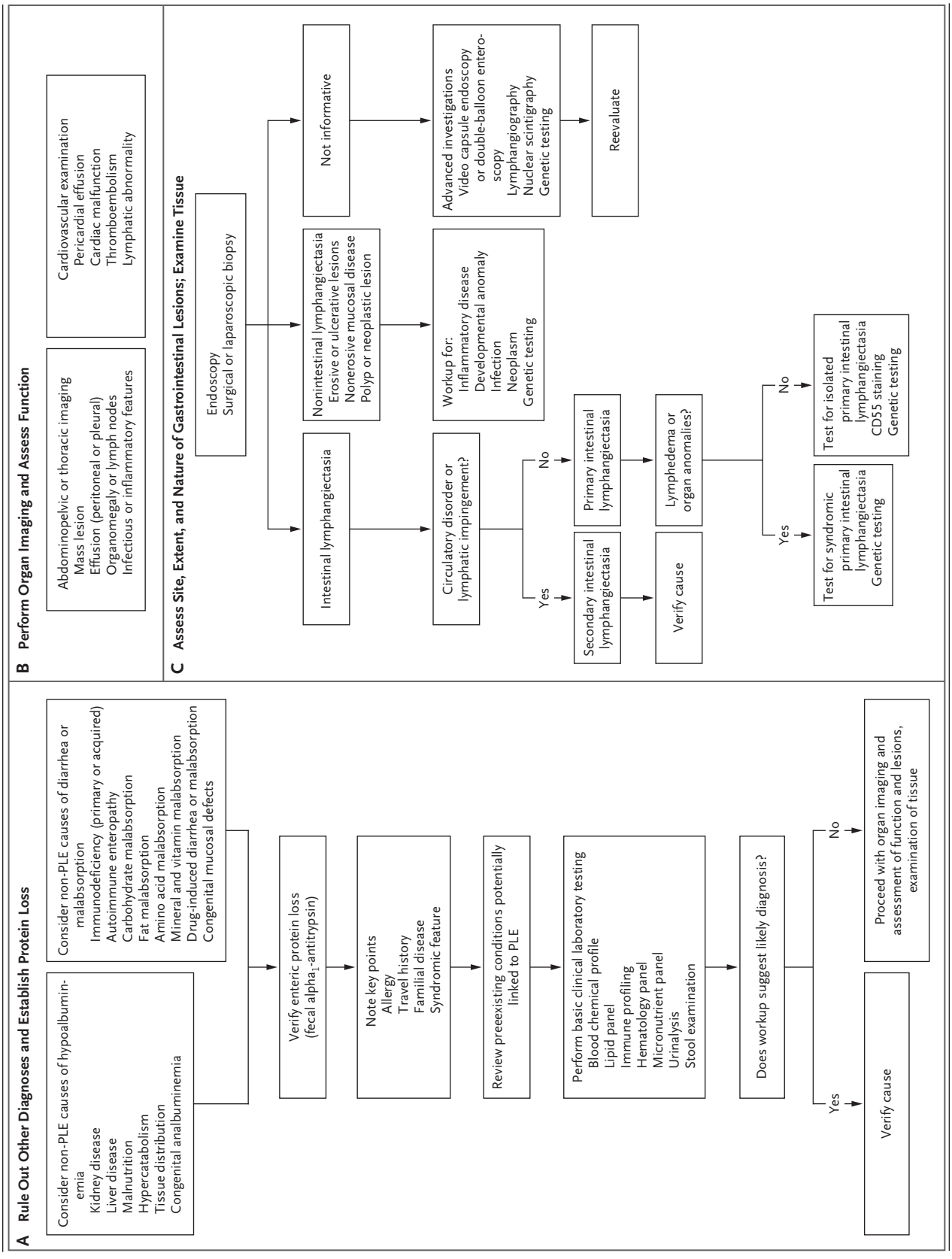

Figure 3 (facing page). Clinical Diagnostic Approach to PLE.

The first step in the diagnosis of PLE is to rule out nongastrointestinal causes of hypoproteinemia and other disorders with similar symptoms (Panel A). Establishing an accurate diagnosis may require a multidisciplinary approach and the use of various diagnostic tools. Clinical laboratory tests provide essential information that directs the evaluation to a particular organ system. Congenital analbuminemia is caused by homozygous or compound heterozygous mutations in the *ALB* (albumin) gene. Noninvasive imaging studies of the thoracic and abdominopelvic cavities and cardiovascular functional assessments (Panel B) or invasive procedures that visualize the digestive tract and obtain biopsy samples for tissue diagnosis (Panel C) may be used for further investigation. Each step in the diagnostic approach focuses on different aspects of the disease to aid in identifying the underlying cause and secondary organ complications of PLE.

disorders causing reduced protein synthesis (e.g., advanced liver disease or malnutrition), increased urinary excretion of protein (e.g., the nephrotic syndrome), increased protein catabolism (e.g., familial hypercatabolic hypoproteinemia), and altered tissue distribution of protein (e.g., increased capillary permeability in the acute phase, with albumin shifted through the interstitial space) should be ruled out.

Gastrointestinal protein loss is assessed by quantitating fecal alpha$_1$-antitrypsin in a random stool sample, or more accurately, by measuring alpha$_1$-antitrypsin clearance in a 24-hour stool collection with simultaneous serum measurement. Alpha$_1$-antitrypsin, a serum glycoprotein, is the same size as albumin, is not actively secreted or absorbed in the bowel, and resists luminal proteolysis in gastrointestinal segments beyond the stomach. Since alpha$_1$-antitrypsin is degraded by pepsin at a gastric pH of less than 3, when gastric protein wasting is suspected, the test is more accurate if performed while the patient is taking acid-suppressing medication.

Syndromic features and a careful clinical history taking (including infectious exposures, travel, and family history) can be useful (Tables 1 and 2). Endoscopy and biopsy can reveal anatomical malformations, obstruction, mucosal inflammation, ulceration, dilated lacteals and lymphangiectasia, and neoplasms (Fig. 3). To evaluate the intestines distal to the ligament of Treitz, video capsule endoscopy or double-balloon enteroscopy is now used.[2] However, because the disease may have a patchy distribution, normal findings on endoscopy or biopsy do not rule out mucosal diagnoses.[1] Abdominal magnetic resonance imaging or computed tomography can be used to visualize the lesions and reveal features that are characteristic of a specific cause. In selected cases with focal intestinal lymphangiectasia, lymphangiography or dynamic contrast-enhanced magnetic resonance lymphangiography may show the site of lymphatic leakage, which could guide interventional treatments. Nuclear medicine studies have been used in rare cases for further characterization but require special radiolabeled proteins and expertise.[3] Congenital protein-losing enteropathy syndromes may also be detected by identifying specific disease components (e.g., lymphedema, atypical facies, or accompanying neurologic abnormalities in the Hennekam syndrome) (Table 2). Molecular investigations, including genomic DNA sequencing, can establish a precise diagnosis. Findings that suggest a hereditary protein-losing enteropathy include a positive family history, an onset of disease at a young age, and parental consanguinity.

MANAGEMENT

The approach to care involves diagnosing and correcting the underlying condition while managing the manifestations of protein-losing enteropathy, principally with treatments that mitigate gastrointestinal protein loss and its sequelae, as well as providing emotional and family support (Table 1, and Fig. S2). Therapies include correction of fluid and electrolyte imbalance, nutritional management, restoration of trace elements, and prevention or control of target organ complications. Additional measures may include support socks to diminish leg edema, antibiotics to control infections, ambulation to avoid venous thrombosis, and skin care to prevent and treat cellulitis, especially when lymphedema is present. Albumin transfusion is indicated for short-term stabilization but typically does not provide a lasting benefit. Immunoglobulin replacement therapy and antibiotic prophylaxis may be used in patients with recurrent infections and profound immunodeficiency.

Dietary changes or drug therapy may alleviate protein-losing enteropathy in some patients. The drugs used for this purpose include octreotide, heparin analogues, antiplasmin therapy, glucocor-

ticoids, sirolimus, and everolimus, but the evidence of efficacy is often inconsistent. Dietary changes can substantially improve certain forms of protein-losing enteropathy and reduce symptoms, especially when a primary lymphatic flow disorder is implicated.[3] A high-protein and low-fat diet (>2 g of protein per kilogram of body weight per day and <25 g of fat per day) with a predominance of medium-chain and short-chain triglycerides may be effective.[2] This modification assumes that the intestinal lymphatic pressure is alleviated because medium-chain triglycerides are directly transported to the portal circulation without assembling into chylomicrons for transport through the lymphatics.[1] Currently, the overall approach is empirical, since evidence-based recommendations cannot be made about symptomatic therapy for most diseases causing protein-losing enteropathy.

Correcting the underlying condition offers the best hope for long-term disease control. For example, if the gastrointestinal lesion can be localized, surgical resection of the affected segment may be effective in patients who do not have a response to medical treatments. In patients with cardiac diseases, specific medical and surgical procedures, including heart transplantation, may be required. New techniques for lymphatic access and imaging enable localization of protein loss through large channels. It is possible to embolize these lymphatic channels by injecting a cyanoacrylate glue.[2]

New gene discoveries have expanded our knowledge of the molecular mechanisms of protein-losing enteropathy, making it possible to provide pathway-specific therapies. A precise molecular understanding may allow repurposing of an approved drug for other indications (off-license or compassionate use) or offer opportunities for testing new drugs for licensure. A good example is eculizumab, a little-used monoclonal complement C5 inhibitor antibody, which can reverse protein-losing enteropathy and restore health in patients with CHAPLE disease.[81] These advances indicate that further molecular investigation will continue to provide new and more precise approaches to the diagnosis and treatment of diseases causing protein-losing enteropathy.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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