Protein-losing enteropathy

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Purpose of review
The present review offers its readers a practical overview of protein-losing enteropathy, particularly with regard to diagnostic and therapeutic approaches. The aim is to support clinicians in their daily practice with a practical tool to deal with protein-losing enteropathy.

Recent findings
The literature covering protein-losing enteropathy does not appear to be quite recent and also guidelines are scanty. The main innovations during the last decade probably regard the introduction of enteroscopic techniques in the diagnostic flowchart. The use of video-capsule and device-assisted enteroscopy has enabled the direct exploration of the small bowel and the identification of the damage causing the loss of proteins from the gastrointestinal tract. Other innovations are to do with the therapies of the disorder underlying protein-losing enteropathy, although the support with nutritional supplementation are the direct remedies to tackle the protein loss.

Summary
Protein-losing enteropathy represents an important clinical aspect of different gastrointestinal and extra-intestinal diseases. An established flowchart is still unavailable, but the use of enteroscopy has deeply changed the modern diagnostic approach. Nutritional support and therapy of the underlying disease are pivotal to patients' management.

Keywords
enteroscopy, hypo-albuminemia, protein-losing enteropathy, small bowel

INTRODUCTION

Protein-losing enteropathy (PLE) is a relatively rare condition determined by excessive protein loss in the gastrointestinal lumen: PLE frequently underlies gut or nongut pathologies [1]. This epiphenomenon is described as an important cause of severe morbidity and increased mortality in certain clinical scenarios [2].

In the current state of the art the epidemiology of this condition is not clearly defined, because of the lack of systematic screening and a wide variety of causes for hypo-proteinemia [3].

Although there are quite a few studies concerning the clinical manifestations of PLE in various diseases, most knowledge on this disease is based on authoritative work [2,3,4–7].

Moreover, not even a precise definition is available and, to our knowledge, no specific cut-off values of hypo-proteinemia have yet been identified. There is still confusion and uncertainty about the actual role played by PLE in the pathological course of the underlying illness; PLE does not seem to worsen the prognosis, but more often it is considered as a marker of worsening of the underlying pathology [2,3].

The aim of this review is to offer a practical overview of PLE, especially for what concerns the diagnostic and therapeutic approaches.

PATHOGENESIS AND UNDERLYING DISEASES

Patho-physiological processes

Albumin leaked through the gut justifies the 2–5% of the total body albumin catabolism. However, in case of PLE such an amount can reach up to the 60% of the total albumin pool [3,8,9]. It is generally accepted that albumin loss through the gastrointestinal tract

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KEY POINTS

- Protein-losing enteropathy is a clinical condition caused by different gastrointestinal diseases.
- No guidelines about protein-losing enteropathy are currently available.
- Treatment should aim at treating the underlying disease and supporting the patients.
- The evaluation of the gastrointestinal mucosa through device-assisted and capsule enteroscopy has become central in the diagnostic flowchart of protein-losing enteropathy.

has to rise up to 17 times the normal rate to lower its blood concentration by half [3].

The blood levels of albumin have been set as a clinical reference to estimate the degree of protein losses. In healthy individuals, albumin is synthetized by the liver and its catabolism accounts for 90% of the clearance of this molecule. Under physiological conditions, gastrointestinal and urinary losses account for respectively 4 and 6% of the clearance. The half-life of albumin is reached in about 17.3 days and roughly 8.5% of serum albumin is replaced every day. In addition, to prevent albumin from degradation, immunogenic processes [binding to the fragment crystallizable (Fc) IgG receptor] are implemented in case of enhanced gastrointestinal or urinary losses [2,10].

As a matter of fact, at the core of this system is the balance between protein synthesis and metabolism. This fine equilibrium is frequently altered in gut and nongut diseases, although it seems that a threshold is required to manifest clinical symptoms [2].

Almost all the blood proteins can be involved in the course of PLE; however, medium or long half-life serum proteins, such as albumin, immunoglobulin (IgM, IgA and IgG, but not IgE), fibrinogen, lipoproteins, alpha-1 antitrypsin (A1AT), transferrin, and ceruplasmin, are most frequently involved. In spite of the loss of serum gamma globulins, the risk of infections does not significantly increase [1]. Lymphocytopenia might occur, particularly in the setting of lymphatic obstruction. In case of small-bowel mucosal disorders (e.g. coeliac disease, primary intestinal lymphoangioectasia), there may be fat malabsorption with related steatorrhoea and fat-soluble vitamins deficiencies [3,6]. Sometimes, the loss of long half-life serum proteins is reflected by a possible increased serum concentration of rapid turn-over proteins, such as prealbumin, IgE and transthyretin [3]. PLE has not been generally linked with any hyper-coagulable state and, to the best of our knowledge, there are only a few studies that have associated PLE with thrombosis [11]. Thus, antiplatelet agents or anticoagulant drugs are not warranted.

More than 60 different illnesses have been related to PLE (Table 1). Almost all the gastrointestinal diseases might be associated with protein loss (frequently clinically silent). Simplifying, gastrointestinal and non- gastrointestinal PLE conditions can be divided into three main groups, following the main patho-mechanism [1]: diseases with

Table 1. Disorders associated with protein-losing gastroenteropathy

Main pathomechanism		
	Intestinal barrier defect	
Increased interstitial pressure	**Erosive mucosal diseases**	**Leaky gut conditions**
Intestinal lymphangioectasia (Congenital, acquired)	Crohn's disease	Coeliac disease
Neoplasia involving mesenteric lymph nodes or lymphatics	Ulcerative colitis	Whipple's disease
Fontan procedure	Intestinal lymphoma	Tropical sprue
Portal hypertension secondary to liver disease or portal vein obstruction	Clostridium difficile, Shigella	Collagenous colitis
Systemic lupus Erythematosus	Ulcerative jejunoileitis	Menetrier's disease
Constrictive pericarditis	GI malignancy	Acute viral gastroenteritis
Congestive heart failure	Erosive gastropathy	Connective tissue disorder
Sclerosing mesenteritis	Sarcoidosis	Small intestinal bacterial overgrowth
	Amyloidosis	Systemic lupus erythematosus
	Nonsteroidal anti-inflammatory drug enteropathy	Cobalamin deficiency

Note: Pathologies associated to high pre-test probability of protein-losing gastroenteropathy are underlined.

increased lymphatic/interstitial pressure; erosive/ulcerative mucosal diseases; and nonerosive mucosal diseases (leaky gut conditions), being the two last related to a defect of the intestinal barrier. However, the overlap and the multifactorial aspects of PLE dominate its patho-physiology, included malabsorption. Furthermore, this classification does not take into account any super-imposed pathological mechanisms that worsen protein loss. Brush border damage and para-cellular leakages are associated with diminished nutrients intake, thus giving relevance to intestinal malabsorption. Intrinsic defects of tight junction permeability in coeliac disease account for both the initial pathogenic stimulus and the following protein loss. It is clear that many pathways contribute to the genesis of PLE and it is not always possible to trace each element back [12]. However, some recurrent histological and laboratory characteristics and patterns can be recognized.

Increased interstitial pressure

First, we have analysed those diseases whose primary impairment is caused by increased pressure whether by venous or lymphatic engorgement. In these cases, the imbalance in Starling forces is the most important but not unique causative agent [2]. In fact, PLE is rarely observed in common diseases with increased capillary and lymphatic pressure, such as heart failure or constrictive pericarditis. The association of PLE and increased lymphatic pressure is known in a particular subset of patients who underwent Fontan surgery, which is the by-pass of a single hypo-plastic ventricle by linking directly the inferior *vena cava* to the pulmonary artery. As a result, the pressure in lymphatic vessels increases. PLE has been extensively studied in such patients as its development has been associated with higher mortality [2,7,14]. On the contrary, PLE in the settings of heart failure does not worsen morbidity nor mortality [15]. Intestinal lymphangioectasia is characterized by a primary damage of the intestinal lymphatic vessels. This anomaly results in an atypical dilation and progressive rupture of these structures, causing the loss of protein-rich fluid. Intestinal lymphangioectasia may be primary (Waldmann's syndrome) or a component of genetic syndromes (Hennekam, Noonan, Turner, Von Recklinghausen, Klippel-Trenaunay) [2]. In this cluster of diseases, long-chain fatty acids are the main responsible for lymphatic drainage failure and the following malabsorption and protein loss [16].

Diseases with increased lymphatic pressure are characterized by common laboratory findings, such as severe hypo-albuminemia (<2 g/dl), low immunoglobulin levels and low CD4 count. From the clinical viewpoint there may be evidence of altered cellular immunity. Interstitial oedema and dilated sub-mucosal lymphatic vessels are usually reported at histology [13].

Intestinal barrier defects: erosive mucosal diseases and leaky gut

Increased mucosal permeability is the main pathogenic process of PLE in diseases with mucosal erosion. Crohn's disease is the classical paradigm for these illnesses [17]. The mucosal barrier damage allows interstitial proteins to freely leak in the mucosal lumen.

Tight junction complex defects are the main cause of the leaky-gut PLE condition. The leakage from para-cellular spaces accounts for protein losses especially in coeliac disease. These tight junction defects seem to exist even in Whipple's disease (marked hypo-albuminemia) and PLE associated to systemic *lupus erythematosus* (SLE) [2].

Menetrier's disease is the first pathological condition where PLE was observed. Currently, the cause of this illness has not been completely clarified, because distinct treatments towards suspected causative agents (*Helicobacter pylori*, epithelial growth factor, transforming growth factor) have been all inconsistent [18]. Gastric PLE requires particular caution at diagnosis because classical quantitative clinical testing might not work because of high acid secretion [2].

CLINICAL FEATURES

PLE is a multifaceted condition, particularly as concerns its clinical presentation. PLE typically manifests with hypo-proteinemia and generalized oedema. Some other signs and symptoms (pericardial and pleural effusion, malnutrition, anasarca, unilateral oedema in case of lymphangiectasia, macular oedema with reversible blindness and retinal detachment) have been described in the literature, but they are less frequent [1,3,19]. Gastrointestinal symptoms such as diarrhoea are frequent but not always present. Nevertheless, the main clinical features reflect the underlying pathology, which implies that the clinical presentation of patients affected by PLE is variable [1,3].

When evaluating a patient with suspected PLE it is essential to take the whole clinical picture into account, the overlap of the underlying mechanism being always present.

DIAGNOSIS

Over the years, many clinical tests have been validated for PLE diagnosis. A quantitative approach

was described by Waldmann *et al.* [20] for the first time in 1961, that is the measure of foecal excretion of ^{51}Cr-albumin [2,21]. Although considered the gold standard, this test appears complex, difficult to set and to perform, and therefore rarely carried out in clinical practice [2]. Other diagnostic radiolabelled tools are theoretically available and some studies have shown their usefulness for the diagnosis and monitoring the response to treatment [22,23]. However, these tests are not widely available and are confined to research purposes.

In the current state of the art, no clear and shared guidelines are available for the diagnosis of PLE. The most commonly used and reliable method to diagnose enteric protein loss is the clearance of α_1-antitrypsin (A1AT) from plasma, which is obtained by the ratio of 1-day stool quantity to the serum levels of A1AT. Normal average A1AT clearance is 20 ml/24 h or less [2,3,24,25]. However, in real-life clinical practice such a method shows little benefit for the clinical management and it is not generally used. Nonetheless, such a technique is burdened by technical and clinical limitations.

Recently, the role of MRI in the diagnosis of PLE has been also studied. Notably, it appeared to be capable of detecting abnormal findings, such as mesenteric/intestinal swelling and lymphatic dilation, in the setting of children affected by lymphangiectasia. In the diagnostic work-up, MRI could be used to support the diagnosis of PLE in an appropriate clinical setting, giving the chance to avoid invasive testing, such as endoscopy and/or biopsy [26].

As reported before, since many gastrointestinal diseases can present with PLE, such diagnostic tests should not be performed when the pre-test probability of PLE is high (see Table 1). In such cases, quantitative measurements should be regarded as a tool to quantify the magnitude of protein loss rather than as a diagnostic approach.

A simplified diagnostic work-up is proposed in Fig. 1. First of all, non-gastrointestinal causes of hypo-proteinemia should be ruled out. Easy-to-access, everyday diagnostic tools (e.g. urine and blood tests, abdominal and heart ultrasonography) should be performed in order to exclude renal and hepatic causes of low proteinemia. ECG and echocardiogram should be first-step examinations to rule any cardiac causes of PLE in or out. BMI and caloric intake must always be taken into account for every patient presenting with low serum proteins. Second, when other illnesses are excluded, A1AT stool clearance may be performed in low pre-test probability scenarios in order to rule PLE in or out, whereas in high-probability settings this procedure is meant to evaluate protein loss or to potentially detect any improvement or worsening.

However, the accurate assessment of signs and symptoms must not be neglected as the clinical presentation itself often guides the diagnosis.

In case of a negative A1AT clearance test, gastric causes, such as Menetrier's disease, should always be taken into account, as AIAT breaks down in acid environments.

Once PLE diagnosis is established, a precise evaluation of gastrointestinal mucosal or lymphatic

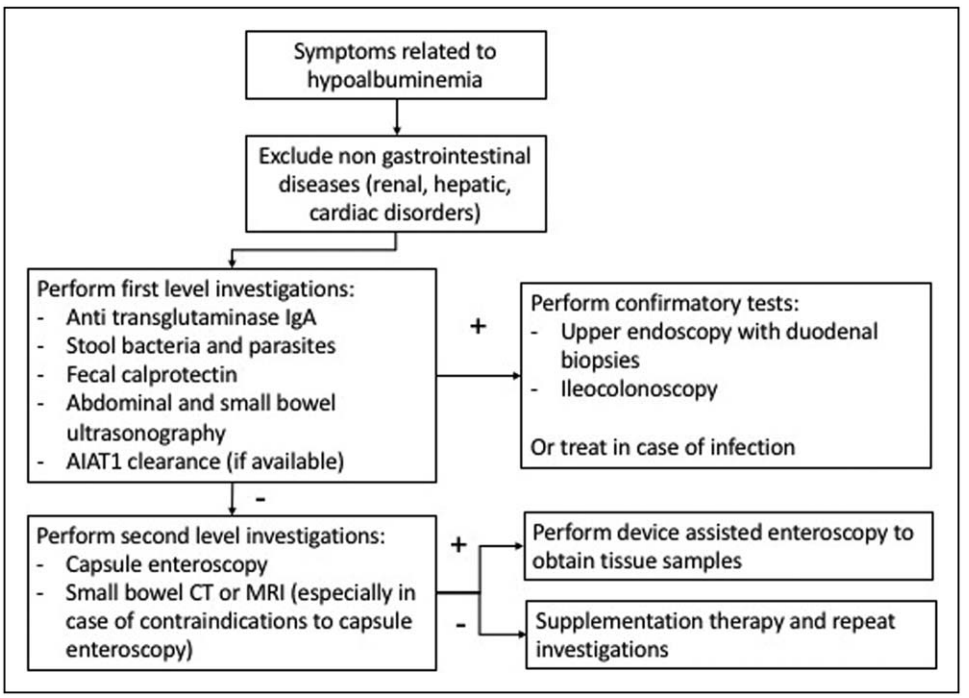

FIGURE 1. Diagnostic roadmap in case of suspected PLE.

disease is recommended. Firstly, we suggest performing a sample blood test for coeliac disease and immune disorders, stool cultures for bacteria and parasites and foecal calprotectin. Imaging studies may be helpful in determining the exact site of protein loss along the gastrointestinal tract. When feasible, abdominal ultrasonography or small intestine contrast ultrasonography may be performed before other radiographic studies (CT/MRI) [27].

Afterwards, we recommend an endoscopic test to directly assess the intestinal mucosa. Endoscopy enhances the chance of finding the cause of protein loss through the recognition of the typical patterns of many diseases, such as any giant rugal folds in the stomach as in Menetrier's disease, or the presence of tortuous, dilated lacteals in the mucosa and sub-mucosa in case of lymphangioectasia. Depending on the findings from the clinical presentation and first-level examinations, oesophago-gastro-duodenoscopy or colonoscopy may be carried out. In absence of clear hints regarding the upper or lower- gastrointestinal localization of the disease, an overall assessment of small-bowel diseases is generally recommended.

Different guidelines [28,29] recommend videocapsule endoscopy (VCE) as the first-line tool for small bowel mucosa visualization. Device-assisted enteroscopy (DAE) is another recent endoscopic innovation that allows both diagnostic (e.g. biopsies) and therapeutic (e.g. balloon-dilations, hemostasis) procedures [30]. Nevertheless, DAE is more invasive and difficult to access and perform than VCE. Therefore, it is recommended as a second-line tool, when a biopsy is needed to confirm the diagnosis or for therapeutic purposes. Figure 2 depicts the enteroscopic appearance of small-bowel mucosa in three disorders usually leading to protein loss.

In conclusion, our suggestion is to bear the clinical presentation in mind and to focus on the high or low probability of PLE in order to tailor the diagnostic work-up to each individual patient's syndrome.

TREATMENT

As we have earlier highlighted, PLE is still shrouded in mist for many aspects. It is noticeable that the most prominent European and American guidelines for the pathologies mainly associated with PLE, that is inflammatory bowel diseases (IBD), coeliac disease and so on [31,32] lack of indications regarding such a condition.

The gap concerns not only the diagnostic work-up, but also the particular treatment for PLE. Specifically, the use of albumin infusion is debated. Neither the guidelines concerning the use of therapeutic albumin nor the ones about main pathologies connected to PLE, offer a clear and demonstrated therapeutic approach to specifically address PLE and its complications. What is certain is that the core of the treatment is to target the underlying chronic pathology [1]. However, when PLE is an acute, severe state, the vagueness of the therapeutic approach is even greater.

The normal daily protein intake is about 0.6–0.8 g/kg of body weight, but in PLE such a necessity may increase up to 2–3 g/kg of body weight in order to overcome the increased protein loss and maintain a neutral protein balance. In order to increase a patient's protein intake, a high-protein diet and the use of commercially available protein supplements are usually sufficient to overcome any enhanced catabolism and losses. In severe malnutrition, parenteral nutrition with a high amino acid intake may be considered, bearing in mind that low oncotic scenarios are associated with the development of oedema [3]. Serum albumin concentration is found to have a prognostic role because of its strong correlation with overall mortality of apparently healthy individuals. However, it is still unclear

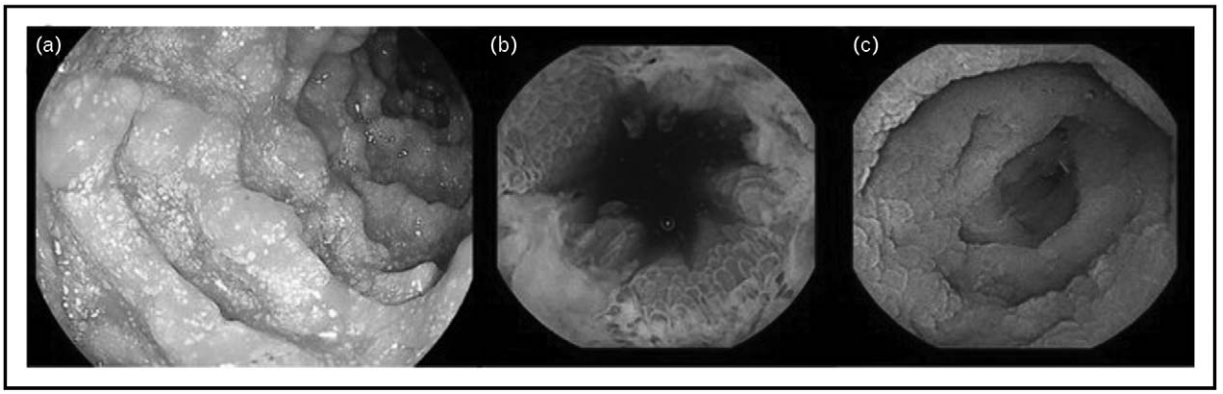

FIGURE 2. Enteroscopic appearance of intestinal lymphangectasia (a) with the typical white-tipped *villi* and white mucosa, Crohn's disease (b) presenting deep ulcers and erosions and coeliac disease (c) with diffuse signs of atrophy.

if low albuminemia accounts itself for increased mortality or it reflects a selection bias: severe clinical conditions are usually associated to low oncotic pressure [2].

Notably, the guidelines of common and relevant gastrointestinal diseases fall short with regard to the approach to PLE. The European Crohn's and Colitis Organization guidelines [31], the ESPEN ones [33–35] and the European Society for the Study of Coeliac Disease (ESSCD) [32] do not focus on the approach to augmented gastrointestinal protein losses. Indeed, many studies show how the administration of human serum albumin (HSA) to treat hypo-albuminemia not associated with hypovolemia is its most common inappropriate use. Critically ill patients represent the only setting in which HSA's use is warranted, with the purpose to correct hypovolemia and fluid depletion rather than improving oncotic pressure *per se*. Anyway, the use of HSA is generally regarded as unhelpful in the long term [36,37].

In the setting of increased lymphatic pressure, there is evidence on the efficacy of a low-fat diet enriched with medium-chain triglycerides (MCTs). In fact, as medium-chain triglycerides are absorbed directly into the portal stream, they reduce the involvement of the lymphatic system of the gut. While for many patients such a diet represents the main method of treating the symptoms of lymphangiectasia, some other patients do not experience any improvement. However, MCTs may not be tolerated by patients; they have a strong odour, are extremely flammable and relatively expensive [40].

Some reports suggest a therapeutic role of octreotide, a somatostatin analogue [38] and intra-venous heparin [39] in PLE. However, the use of these drugs relies merely on case reports and the mechanism of their action is not generally understood. Somatostatin analogues may have an effect on lymph fluid excretion, digestive fluid secretion and partially on portal pressure. The mechanism of action of heparin is poorly understood; it seems that heparin might play a role as a similar substrate to glycosaminoglycans in the enterocytes [38,39]. As anticipated before, PLE is not associated to hyper-coagulability state. Therefore, the therapeutic plans do not usually include antiplatelet agents or anticoagulant drugs.

At last, adequate physical exercise, ambulation and support stockings are helpful in reducing peripheral oedema and preventing venous thrombosis.

Particular attention should be paid to the cutting-edge therapies for specific diseases as they might have a substantial effect on PLE too. Larazotide acetate, a novel tight junction inhibitor, has proved its efficacy in treating coeliac-associated symptoms in phase I and phase II clinical trials. This drug promotes tight junction integrity: this poses a question regarding its hypothetic use in preventing para-cellular leakage in protein-losing enteropathy [41].

CONCLUSION

Protein-losing enteropathy is a clinical condition that may be associated with different gastrointestinal diseases and non-gut conditions. Its diagnosis is mainly based on the high clinical suspicion and exclusion of other causes of low oncotic pressure (hepatic synthesis, renal losses). Specific clinical tests are available to confirm or rule this illness out, but they are not generally performed.

Overall, there is paucity of guidelines addressing PLE and enteric protein losses are not well described and analysed in the guidelines on common gastrointestinal disorders, such as coeliac disease and IBDs. Protein-losing enteropathy treatment is mainly pointed towards the underlying disease.

A generally shared approach to this specific disease is still missing, and further studies are recommended to estimate the prevalence of PLE and its effect on clinical management.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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