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Protein-Losing Enteropathy Following Fontan Palliation

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ABSTRACT

Protein-losing enteropathy (PLE) is a chronic condition involving multiple organ systems that may develop any time following Fontan completion. The pathogenesis of PLE is complex and multifactorial. Chronic venous hypertension, low cardiac output, and abnormal lymphatics may all play a role in the pathogenesis of PLE. Common signs and symptoms include chronic diarrhea, abdominal pain, and ascites. Diagnosis is based on the presence of signs and symptoms in addition to hypoalbuminemia and elevated stool alpha 1 antitrypsin. Early identification and a comprehensive approach to evaluation and treatment are important, as they may affect survival. The initial evaluation should include cardiac catheterization for hemodynamic assessment. Although an evidence base for treatment is lacking, various medical, interventional, and surgical approaches have been described with variable degrees of success. Commonly used therapies include

RÉSUMÉ

L'entéropathie exsudative est une maladie chronique touchant plusieurs organes qui peut apparaître à tout moment après une intervention de Fontan. La pathogenèse de l'entéropathie exsudative est complexe et multifactorielle. L'hypertension veineuse chronique, un faible débit cardiaque et des vaisseaux lymphatiques anormaux pourraient tous jouer un rôle. Les signes et symptômes courants comprennent la diarrhée chronique, la douleur abdominale et l'ascite. Le diagnostic repose sur la présence de signes et de symptômes, ainsi que sur une hypoalbuminémie et un taux élevé d'alpha-1 antitrypsine dans les selles. La détection précoce et une approche exhaustive de l'évaluation et du traitement sont cruciales; la survie du patient peut en dépendre. L'évaluation initiale doit comprendre une cathétérisation cardiaque afin de déterminer les paramètres hémodynamiques. Même si on dispose de peu de données probantes permettant d'établir un

Protein-losing enteropathy (PLE) post-Fontan palliation is one of the most challenging complications encountered by persons living with a univentricular circulation. A commonly used definition for PLE is the presence of hypoalbuminemia (<30 g/L) with no other identifiable mode of protein loss other than the gastrointestinal tract.[1] The disease is heterogenous, and patients often have a relapsing and remitting course. Typical clinical manifestations include chronic diarrhea, abdominal pain, ascites, effusions, and peripheral edema. Onset of symptoms varies from a few weeks to years following Fontan completion. Affected patients may also develop secondary manifestations related to loss of enteric proteins, including hypocalcemia, sepsis, and growth failure. Hypoalbuminemia, in the absence of symptoms, is another possible initial presentation.

The incidence of PLE in the Fontan population is approximately 4%.[2] Mortality was previously reported as high as 50% at 5 years.[2] However, more contemporary data from the Mayo Clinic report improved survival of 88% at 5 years after the diagnosis and 72% at 10 years,[1] likely due to earlier diagnosis and comprehensive care.

Pathophysiology and Risk Factors

The etiology of PLE post-Fontan is unknown. There are several pathophysiological mechanisms that may be responsible. Chronic low cardiac output and systemic venous hypertension are inherent with the Fontan circulation. PLE has been described in other conditions characterized by chronic elevation of systemic venous pressure, such as constrictive pericarditis or an obstructed Mustard/Senning IVC baffle. Any factor resulting in increased systemic venous pressure will predispose patients with a Fontan to develop PLE. This includes Fontan pathway obstruction, pulmonary artery branch stenosis, increased pulmonary vascular resistance, elevated atrial pressures related to AV-valve regurgitation, arrhythmias, and diastolic dysfunction. Furthermore, low cardiac output may increase mesenteric vascular resistance and lead to decreased intestinal perfusion, compromising gut mucosal integrity.

Recent developments have also shed light on the important role of lymphatics in this disorder. Elevated systemic venous

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nutritional support, diuretics, subcutaneous unfractionated heparin, budesonide, and sildenafil. Limited data exist for Fontan conversion or takedown. Assessment for heart transplantation should be considered. PLE mortality is high—approximately 50%—but may be mitigated by aggressive investigation and management. The evolving understanding of the role of lymphatics in the pathophysiology of PLE and the emerging role of interventional lymphatic procedures may further improve outcomes in this patient population.

plan de traitement, différentes approches médicales, interventionnelles et chirurgicales ont été employées avec plus ou moins de succès. Les traitements le plus couramment employés comprennent le soutien nutritionnel, les diurétiques, l'héparine non fractionnée administrée par voie sous-cutanée, le budésonide et le sildénafil. Les données sur l'efficacité de la correction ou du démontage de la chirurgie de Fontan sont limitées. Il convient d'envisager l'admissibilité du patient à une greffe cardiaque. Le taux de mortalité associé à l'entéropathie exsudative est élevé (environ 50 %), mais le risque peut être atténué grâce à une évaluation et à une prise en charge dynamiques. L'évolution des connaissances quant au rôle des vaisseaux lymphatiques dans la physiopathologie de l'entéropathie exsudative et l'importance émergente des interventions touchant ces vaisseaux pourraient contribuer à améliorer les résultats pour cette population de patients.

pressure causes an increase in lymphatic hydrostatic pressure, which subsequently increases lymph production. For example, in patients with PLE post-Fontan, leakage of liver lymph through dilated hepatoduodenal lymphatic connections into the duodenum has been demonstrated, using a combination of duodenoscopy and hepatic lymphangiography.[3] As all patients with Fontan have elevated venous pressure, it remains unclear why only 4% of all with Fontan develop PLE.

Establishing risk factors for PLE post-Fontan completion is difficult, as the disease is rare, and therefore a large Fontan cohort to establish risk factors is needed. Heterogenous single ventricle anatomy and evolving surgical approaches to Fontan completion also complicate the identification of risk factors. In the Mayo Clinic experience, patients with PLE and elevated pulmonary vascular resistance or low cardiac output had higher risk of mortality.[1] However, it is not uncommon to see a patient with excellent Fontan hemodynamics who develops PLE. Likewise, many patients who have borderline Fontan hemodynamics do not develop PLE. These observations are consistent with the complex pathophysiology of PLE.

Clinical Evaluation

The diagnosis is made by the demonstration of clinical manifestations and enteric loss of protein through elevated stool alpha 1 antitrypsin (a1AT). Elevated a1AT can be demonstrated with either a spot stool sample or 24-hour collection of stool; there are no data that either method is superior. There is considerable variation in the reported normal range for the spot fecal a1AT concentration (1 to 3 mmol/L) and clearance (12.5 to 50 mL/24h). There is variability in the laboratory cutoff values that have been used in published definitions of PLE. Stool a1AT level may be low (false negative) in PLE if the primary loss is from the stomach, whereas in patients with diarrhea, the levels may be falsely high (false positive). Low normal levels of serum albumin or stool fecal a1AT do not exclude a possible diagnosis of preclinical PLE.

A comprehensive multidisciplinary approach to evaluation should be promptly initiated to address any correctable factors and assess the severity of the disease (Fig. 1). The initial evaluation should search for factors that may increase systemic venous pressure. Echocardiography and cardiac magnetic resonance imaging (MRI) may identify obstruction in the Fontan pathway or pulmonary artery stenosis. A 12-lead electrocardiogram and Holter monitor are important to assess for arrhythmias that may lead to loss of atrioventricular synchrony and low cardiac output. In addition, cardiac catheterization for hemodynamic and anatomical assessment is important to identify elevated Fontan pressure, Fontan or pulmonary artery obstruction, elevated pulmonary vascular resistance, and to measure cardiac output. Rapid volume expansion during cardiac catheterization may identify occult diastolic dysfunction, which may not be present on standard hemodynamic assessment. MRI lymphangiogram should be considered to assess for abnormal lymphatics. Liver lymphangiography to identify abnormal hepatoduodenal connections has recently been described.[3] Renal and liver function can be affected in patients with PLE due to the disease process and/or chronic medical therapy, and therefore a renal and liver assessment is an important part of initial evaluation and ongoing management. Exclusion of other causes of hypoalbuminemia, such as other gastrointestinal problems or nephrotic syndrome, should also be performed.

Treatment

As PLE is uncommon, the literature is limited to case reports and small observational studies. Rigorous evidence-based therapy is lacking. In general, management should aim to minimize symptoms and the side effects of therapy and improve quality of life. Treatment options include medical, interventional, and surgical approaches.

Most patients will require hospital admission for initiation and monitoring of treatment. Diuretics and albumin infusion are commonly prescribed to address fluid overload and intravascular volume depletion. Nutritional support is important, as these patients are at risk of malnutrition. The use of a high-protein diet ($\geq$ 2 gram/kg/d) and low-fat diet ($\leq$ 25% of caloric intake), along with medium-chain triglyceride supplementation, has been recommended to reduce the amount of enteric protein loss and improve nutritional status.[1] Medium chain triglyceride supplements bypass the disrupted lymphatic system, as they are absorbed directly into the bloodstream.

Subcutaneous unfractionated heparin is a common therapy with various degrees of success.[1] The pharmacological basis is not well understood, but it is thought that heparin restores

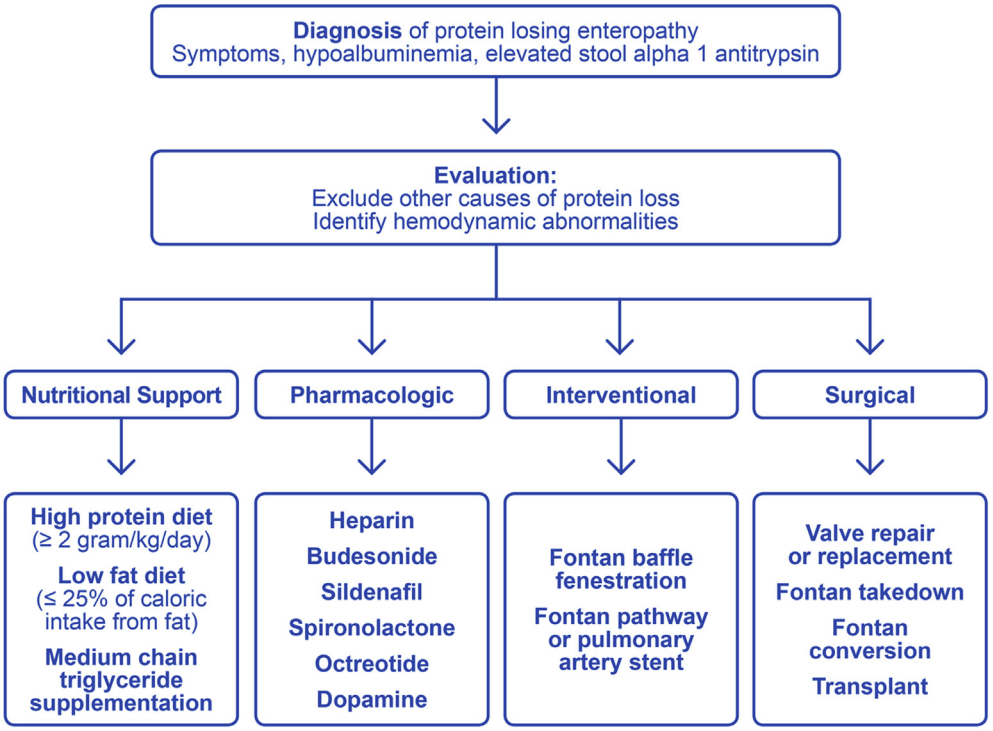

Figure 1. Suggested approach to PLE investigation and management.

luminal basal membrane integrity and restoration of heparan sulphate, which is an important component of intestinal membrane permeability. In addition, heparin prevents formation of microthrombi in the mesenteric vascular bed and therefore may lower mesenteric vascular resistance. Budesonide is an enteric-specific steroid, which has been used for its anti-inflammatory effect. It is important to ensure normal liver function before starting budesonide, as this drug is metabolized by the liver.

A variety of other therapies have been used in patients with PLE (Table 1). For example, medications used more frequently in survivors vs. nonsurvivors at the Mayo Clinic were spironolactone, octreotide, and sildenafil.[1] Spironolactone may benefit this population through its diuretic effect, improvement of ventricular function, or its association with improved endothelial function and reduced inflammation. Octreotide reduces lymphatic flow and may mediate its effect through this mechanism. Sildenafil lowers pulmonary vascular resistance, which, if elevated, will contribute to lower cardiac output. Dopamine has resulted in improvement of PLE symptoms.[4] The mechanism has been attributed to improvement in lymphatic circulation, owing to the effect of dopamine on lymphatic receptors rather than its inotropic effect. Intravenous immunoglobulin can be used to replace lost immunoglobulins and potentially decrease the risk of infections, although data to support this approach are limited. Most recently, biphasic cuirass ventilation was reported to result in improvement in symptoms in a patient with plastic bronchitis and PLE.[5] Evidence-based data evaluating these therapies are lacking, and multicentre studies are needed to have sufficient sample size and statistical power.

Table 1. Medical therapy in protein-losing enteropathy

Pharmacotherapy	Doses
Furosemide	2 to 4 mg/kg/d orally or intravenously (IV) divided q6h to q12h
Spironolactone	2.5 mg/kg/d orally, divided, twice daily
Albumin (25%)	0.5 to 1 gram/kg/dose IV as needed
Unfractionated heparin	5,000 units/m^2 per day subcutaneously, divided into 2 doses
Budesonide	3 mg orally, 3 times per day
Octreotide	10 mg to 20 mg intramuscularly, once monthly, 50 μg subcutaneously, 3 times per day
Sildenafil	3 mg/kg/d orally, divided 3 times a day
Dopamine	5 μg/kg/min IV

Catheter-based interventional procedures should be considered on an individual basis. Patients with PLE with elevated Fontan pressure and no right to left shunt may benefit from creation of a fenestration in the Fontan baffle, with the goal of decreasing the systemic saturation to 80% to 85%. However, creation of a fenestration carries the risk of stroke and risk of spontaneous closure with recurrence of PLE. In addition, a beneficial response may take 3 to 4 months. Obstruction in the Fontan pathway or pulmonary artery stenosis should be addressed, as this results in elevated systemic venous pressure. If junctional rhythm is present, one should consider atrioventricular pacing, as dysynchrony is poorly tolerated in patients with a single ventricle. More recently, percutaneous embolization of hepatoduodenal lymphatic connections has resulted in relief of symptoms and elevation of serum albumin in a small series.[3]

Surgery may be indicated in patients having hemodynamic problems not amenable to catheter-based therapy, such as atrioventricular valve regurgitation. There is limited experience with Fontan conversion or takedown as treatment for

PLE. Evaluation for heart transplant is warranted, as PLE may resolve following transplantation. In addition, a ventricular-assist device may be considered as a bridge to transplant in selected patients with depressed systolic function and symptoms of heart failure.

Prognosis

Risk factors for death in the setting of PLE include high Fontan pressure (mean >15 mm Hg), ventricular dysfunction (ejection fraction <55%), and New York Heart Association Class III or IV.[1] In the Mayo Clinic experience, patients who died had higher pulmonary vascular resistance, lower cardiac index, lower mixed venous oxygen saturation, and higher serum creatinine. Mortality, although historically as high as 50%,[2] may be improved with earlier diagnosis and aggressive medical and interventional management.[1]

Conclusion

PLE following Fontan palliation is an uncommon yet challenging complication. Early identification and a comprehensive, multidisciplinary approach to these patients may help to improve outcomes. The recent development of lymphatic interventional techniques may benefit this population, although experience to date is limited to very few centres.[3]

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Disclosures

The authors have no conflicts of interest to disclose.

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