Evaluation and Management of Protein Losing Enteropathy in Fontan Patients

ADVANCED CARDIAC THERAPIES IMPROVING OUTCOMES NETWORK

HARMONIZED PROTOCOL

BACKGROUND

The common endpoint of staged surgical palliation for patients with single ventricle physiology is the Fontan procedure. Approximately 5-12% of Fontan patients will develop protein-losing enteropathy (PLE), characterized by the abnormal intestinal loss of serum proteins. It is a potentially devastating disease with 5-year mortality reported as high as 50% after diagnosis. In addition to the extremely high mortality rate, PLE often confers significant morbidity in patients. Although the exact cause of PLE is incompletely understood, abnormal mesenteric resistance, chronic systemic and enteral inflammation, derangement of the lymphatic circulation, and abnormal enterocyte basal membranes all likely play a role in PLE's development and progression. The role of abnormal lymphatic anatomy and function is increasingly appreciated. Regardless of underlying pathophysiology, PLE leads to significant morbidity in Fontan patients. Treatment strategies have evolved over time and have variable reported efficacy, contributing to the challenges in management of these complex patients.

ACTION REVISED DATE: 04/12/2022

OBJECTIVES

To offer standardized guidance for evaluation and management of Fontan patients during initial and recurrent episodes of PLE.

PROTOCOL

1. **Clinical definition of PLE in Fontan patients**
   Concurrent with the enteric loss of protein, patients with PLE present with a history of edema, abdominal distension (ascites), diarrhea, and/or effusions. Patients may also have reduced linear growth velocity with reduced bone density in chronic cases due to disruption in calcium regulation as well as consequence of steroid therapy. PLE patients may have increased susceptibility to infection due to stool immunoglobulin loss and lymphopenia. Laboratory derangements include hypoalbuminemia, hypoproteinemia. Coagulation abnormalities may also be present due to dysregulation of clotting factors which places patients at additional risk of thromboembolic events. PLE is often a chronic disease with a relapsing and remitting clinical course over time.

Hallmarks of PLE presentation:
-low serum albumin
-positive stool alpha-1-antitrypsin
-edema, effusions, ascites, GI symptoms, diarrhea

2. Initial evaluation of PLE

Laboratory evaluation			Diagnostics		Invasive imaging and intervention considerations (patient specific)
Blood			Echocardiogram	Holter monitor	Cardiac catheterization
Albumin	CBC w/diff	LFTs	Electrocardiogram	Cardiac MRI	Lymphangiogram
Total protein	BMP w/Mg	+/- ATIII	CXR (AP & Lat)	+/-Venous US	MRI Interventional radiology
IgG level	INR, PTT	Vitamin D	Abdominal US		
Urinalysis	Stool alpha-1-antitrypsin				

*PLE specific lab work and diagnostic testing should be performed with new diagnosis PLE and then as indicated with recurrence of PLE. Invasive imaging and intervention should be performed on a patient-by-patient basis after initial evaluation.

a. Physical Exam
- height, weight, BMI
- peripheral edema and/or ascites
- muscle wasting
- abdominal distension, hepatomegaly
- pulmonary exam changes consistent with pleural effusion

b. Laboratory evaluation
- Serum albumin
- Serum total protein
- Stool alpha-1 antitrypsin level
  - Ideally collected via 24-hour stool collection (gold standard) but consider spot level in patients in whom 24 collection not possible.
- Complete metabolic profile (CMP) (including serum electrolytes, BUN, creatinine, calcium and magnesium) with inclusion of liver function tests
- Complete blood count with cell differential (CBC w/diff)
  - Assess for anemia and lymphopenia.
- Coagulation studies, including INR and partial thromboplastin time (PTT)
- Serum immunoglobulin G level
- Serum vitamin D level
- Pre-albumin level
- Consider urinalysis, including protein, and urine creatinine
- Consider anti-thrombin III level with history of thrombosis

c. Diagnostic studies
- Echocardiogram to assess current function and structures with particular attention to fenestration status, Fontan flow characteristics, pulmonary vein patency, atrial septum restriction, atrio-ventricular valve regurgitation, ventricular function, and ventricular outflow obstruction.

- Electrocardiogram (ECG) to assess baseline rhythm and serial changes
- Chest X-ray (CXR) with AP and lateral views to assess for pleural effusion and/or pulmonary edema
- Abdominal ultrasound (US) with Doppler to assess for ascites, liver size/architecture/vessel flow, spleen, and evidence of portal hypertension
- Holter monitor to assess baseline rhythm, sinus node dysfunction, occult arrhythmia
- Consider cardiac magnetic resonance imaging (MRI) to further assess function, Fontan circuit, valve function, potential anatomical obstruction
- Consider venous US of upper and lower extremity veins to assess for patency and presence of new narrowing or obstruction

d. Invasive imaging and interventions
    - Cardiac catheterization
        - Measure Fontan pressures, cardiac output, ventricular end-diastolic pressure, and pulmonary vascular resistance, which will help to guide the medical management.
        - Evaluate and possibly to treat any anatomic abnormalities that increase pressure in the Fontan pathway, such as baffle obstruction, pulmonary artery stenosis, and aortopulmonary collaterals
    - Consider lymphangiogram
        - MRI lymphangiogram
        - Interventional radiology

e. Lymphatic Intervention

Patients with PLE recalcitrant to medical interventions may be considered for targeted lymphatic system interventions. These procedures are not widely available at all centers, but play an important role for patients who have failed all other therapies but may not be ideal candidates for heart transplantation.

The Fontan circulation, with its obligate increase in central venous pressure, is accompanied by increased hepatic lymphatic fluid production. This increased lymphatic volume drains via lymphatic channels that connect to the intestinal lumen, usually the duodenum. In addition, increased hepatic lymphatic fluid production may be accompanied by ascites. Both of these mechanisms may be partly responsible for the development of PLE. Hepato-duodenal lymphatic connections can be visualized by intra-hepatic or intra-mesenteric dynamic contrast MR lymphangiography using gadolinium. The presence of such connections can also be proven by intrahepatic lymphatic injection of iosulfan blue, with confirmation of iosulfan blue entering the duodenal lumen via concurrent endoscopy. These connections can then be embolized using glue injected via a transabdominal approach into the hepatic lymphatic channels; improvement or resolution of PLE has been reported in some patients undergoing this procedure.

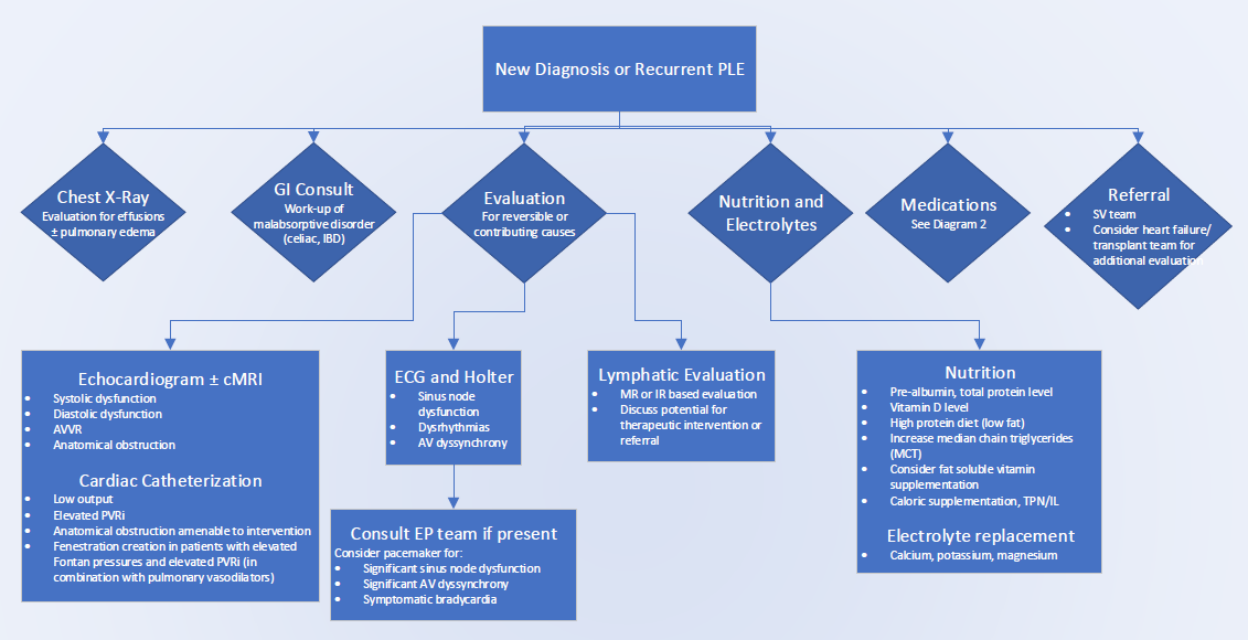
“Rerouting” of the innominate vein (which receives thoracic duct effluent) to a lower-pressure cardiac chamber has also been performed in some patients with severe PLE. In such interventions, the innominate vein drainage is diverted to the left atrium, either via direct surgical anastomosis or by

transcatheter means using a covered stent. This approach appears to be most effective for patients with high transpulmonary gradients.

There are no absolute contraindications to lymphatic intervention. These procedures are not widely available at all centers, but play an important role for patients who have failed all other therapies. The following are relative contraindications or patients in whom lymphatic intervention may be less effective:

- Presence of a permanent pacemaker, which may preclude the ability to perform MR lymphangiography.Direct intranodal lymphangiography using iodinated contrast can be performed as an alternative, but is cumbersome
- Inability to hold anticoagulation for several days post-procedure due to severe thrombotic disease (due to requirement for transabdominal puncture for glue administration)
- Pre-existing pancreatic or biliary disease (also due to requirement for transabdominal puncture)
- Patients who have undergone previous thoracic duct embolization or ligation

f. Expert consultation
   - Dietician to help with initiation of high-protein diet and supplements
   - Hepatology/Gastroenterology with expertise in Fontan population and PLE
   - Electrophysiology (EP) for patient with concern for contributing sinus node dysfunction, arrhythmia and/or significant atrioventricular desynchrony
   - Consider Heart failure/transplant team referral as per ACTION document *"Considerations for Advanced Heart Failure Consultation in Fontan Patients"*



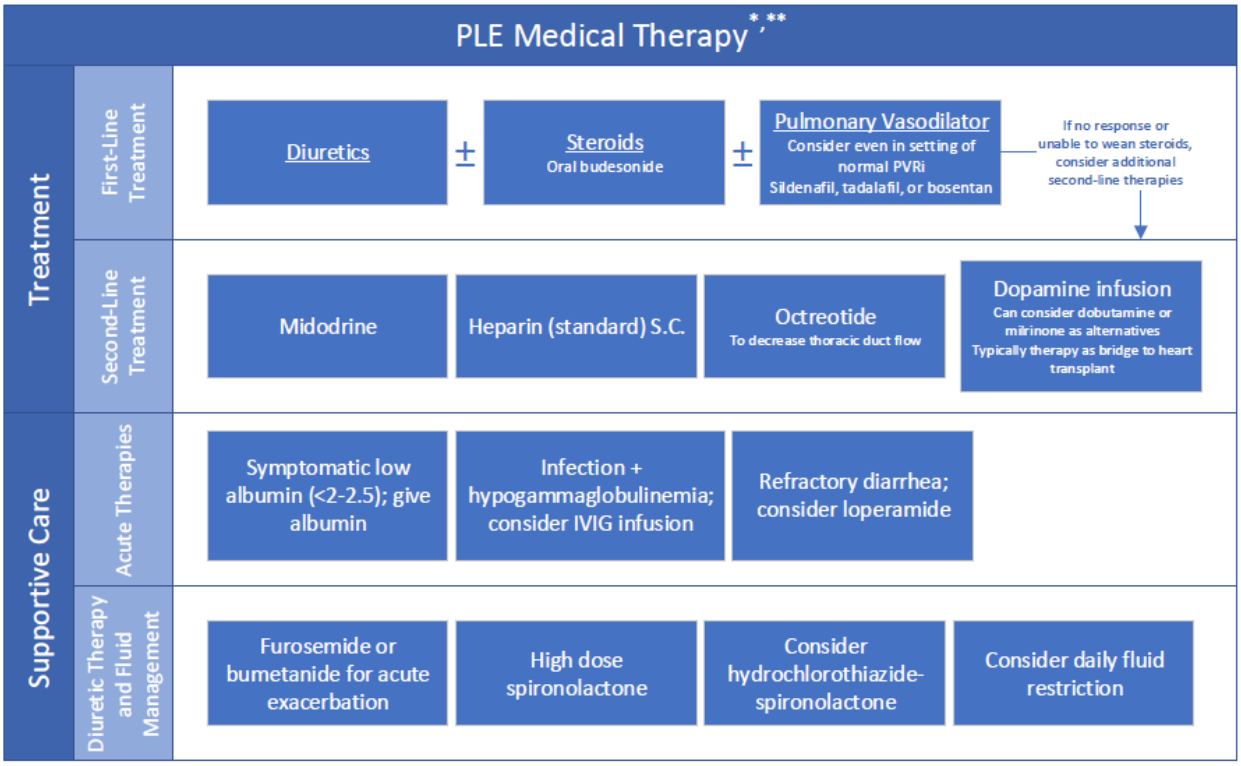
3. **Management of PLE**

Management of PLE includes evaluation for cardiac issues that may be amendable to intervention to optimize Fontan physiology and titration of medical therapy to treat related symptoms. Patients should be evaluated for anatomical lesions that can be treated via cardiac catheterization, dilation/stent of obstruction or embolization of significant collaterals. Patients should also be evaluated for potential venothrombosis given increased risk, particularly in patients with prior history or low ATIII levels. Some patients with identified lymphatic abnormalities may be candidates for lymphatic based interventions. Any rhythm disturbances, such as tachyarrhythmias or bradycardia, should prompt discussion with EP regarding possible anti-arrhythmic or pacing therapy. Medical management focuses on reducing volume overload, improving nutrition, and reduce recurrence. Risk and benefits of potential diagnostic evaluations and treatments presented in this guideline should be discussed in a multi-disciplinary fashion with involvement of the patient and family.

Depending on severity of symptoms and PLE at presentation, patients may require hospital admission for medical therapy, particularly in patients requiring intravenous therapy.

a. Dietary interventions (in consultation with experience dietician)
    - High-protein diet appropriate for age
    - Consider low long chain triglyceride (LCT) diet supplemented with medium chain triglycerides (MCT) may be beneficial if lymphatic abnormalities are contributing to PLE pathophysiology. Decreasing LCT intake theoretically decreases lymphatic flow and pressure which is thought to contribute to decreased losses via gastrointestinal tract. When this therapy is followed, it is crucial to provide adequate LCT, 2-4% of total calories, to prevent essential fatty acid deficiency. A serum triene-to-tetraene ratio can be obtained to assess for essential fatty acid deficiency.
    - Consider supplementation of fat-soluble vitamins in water-soluble forms to account for increased losses via the gastrointestinal tract.
    - In severe refractory cases, may require period of bowel rest and concurrent total parental nutrition (TPN) support
    - Discuss with team (including cardiac catheterization and interventional radiologist) referral for lymphatic intervention

b. Medications



*See suggested dosing in table below. If patient does not respond to first line therapy, discuss second-line therapy treatment strategy with advanced heart function support team.

**Anticoagulation note: Warfarin levels may be affected by albumin infusions given changes in protein bound drug amounts. Caution should be applied in adjusting warfarin dosing in patients on warfarin receiving intermittent albumin infusions.

Medication	Dosing Recommendations	Implications of therapy/clinical pearls
Albumin[1]	1-4g/kg/d divided every 4-6 hours with a goal of increasing serum albumin to ≥3 g/dL.	• Use 25% product • Follow albumin infusion with administration of diuretic such as loop diuretic • Central access not required
Aspirin	Daily 81mg po dosing	• Due to increased thrombosis risk • If thrombosis, consider change to SQ LMWH or warfarin
Budesonide	Oral delayed release capsule: - Children less than 7 years: starting dose 6 mg once daily[2,3] - Children greater than or equal to 7 years: starting dose 9 mg once daily or 3 mg Q8H[4,5]	• Consider "pulse" steroid course of 3-5 days with first or mild PLE episode (some patients may require longer term therapy with taper) • If prolonged therapy: after clinical improvement and albumin greater than 3 g/dL for at least 6 months, then consider wean over several weeks to 3 mg once daily or every other day with goal albumin greater than 2.5 g/dL. Consider completely tapering off in patients with significant side effects.
Dopamine[6]	IV: 3-5 mcg/kg/min starting dose	• May provide benefit outside of improving cardiac function, chronotropy and/or mesenteric blood flow
Dobutamine	IV: 0.5-1 mcg/kg/min starting dose	• Often used as bridge to heart transplant
Furosemide	- IV: 0.5-2mg/kg/dose children, 20-40mg adolescents starting dose - PO: 0.2-2mg/kg/dose children, 20-40mg adolescents - Q6-24 hour dosing	• Titrate dose and frequency to effect. Gradually decrease frequency and dose to minimal effect dose.

	- 2 mg/kg/day reported in PLE (route unspecified)[7]	
Heparin (UFH)[8,9,10]	SQ: 5000 units/m2/day divided BID	• Long term administration (greater than 6 months) can cause bone loss/softening due to a reduction in bone mineral density • Discontinue therapy if no response after trial of 2-3 months • If titrating higher than recommended dosing, consider obtaining UFH level 6 hours after dose given • LMWH does not appear to have the same efficacy/benefit that UFH does for these patients • Contraindicated in patients with recent significant bleeding
IVIG[11]	IV: 1g/kg/dose every 4 weeks *consider higher doses and/or more frequent administration in patients with very low IgG levels	• Consider dose adjustment for obesity (Ideal or adjusted body weight) • Some patients experience infusion site discomfort with peripheral infusion
Loperamide	- Use in children less than2 years generally not recommended - Use age and weight specific dosing	• One case report of use in an adult patient[12] • Use lowest effective dose for shortest duration • Use for PLE beyond 1 month has not been described
Midodrine	Children: starting dose ~0.2 mg/kg/day PO divided TID[13] Adolescent/adult: starting dose 2.5 mg PO two to three times daily[13] Maximum dose: 10 mg PO TID	• CHCO non-formulary medication • Monitor for supine hypertension and bradycardia
Milrinone	IV: 0.25-0.5 mcg/kg/min starting dose	• Caution/adjust dose for renal impairment • Often used as bridge to heart transplant
Octreotide	- continuous IV: 1-2 mcg/kg/hour - IM LAR depot: 10-20 mg monthly reported[14] - IM immediate release: 50 mcg TID reported[14]	• After continuous IV initiation, may convert to subcutaneous injections • May cause hyperglycemia, hypoglycemia, hypothyroidism, cholelithiasis • Cardiac side effects: bradycardia, QT prolongation • Caution/dose adjustment in patients with hepatic impairment
Sildenafil	Infants and children: - Starting dose: 0.5 mg/kg/dose PO every 6 hours reported[15] - Maximum dose: 1.5 mg/kg/dose PO every 6 hours reported[15] - Maximum total daily dose: 60 mg PO Adolescents and adults greater than 45 kg: - Starting dose: 10 mg PO every 8 hours	• Titrate to goal dose over several days • If no improvement within 3+ months, wean off
Spironolactone[16,17,18]	PO/NG/G-tube: 4-6 mg/kg/day divided BID	• Consider transition to eplerenone if gynecomastia develops • Periodic serum potassium checks necessary
Tadalafil	0.5-1 mg/kg/dose once daily. Maximum dose is 40 mg (if tolerated)	• Consider as alternative for sildenafil with once daily dosing in older patients

4. Chronic PLE management

PLE in Fontan patients is often punctuated by exacerbation episodes with or without chronic symptoms. These patients require close monitoring for early intervention and medical optimization. PLE also places Fontan patients at increased risk for non-cardiac sequela which treating providers must be aware of. In some patients, severity

and frequency of symptoms prompts referral for heart transplantation. In general, early referral to the heart transplant team is preferred.

a. Clinic visits
   - Every 6 months for patients with quiescent PLE
   - More frequently for patients with active PLE with consideration of escalation of treatment at each visit

b. Laboratory evaluation
   - Every 3-6 months early after diagnosis and then at least annually: BMP, Magnesium, LFTs, CBC, albumin, total protein

c. Diagnostic testing (in addition to routine cardiac testing for Fontan population
   - Consider DEXA-bone scan bi-annually in patients at high risk for or with prior h/o osteopenia

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