Protein-Losing Enteropathy and Plastic Bronchitis After the Fontan Operation

Christine Peyton, MS, CPNP-AC, CCRN

Protein-losing enteropathy and plastic bronchitis remain challenging to treat despite recent treatment advances. Protein-losing enteropathy and plastic bronchitis have been diagnosed in patients with cardiomyopathy, constrictive pericarditis, and congestive heart failure. This article focuses on patients with protein-losing enteropathy or plastic bronchitis following the Fontan procedure. Patients with single-ventricle physiology who have undergone the Fontan procedure are at risk for these conditions. Fontan physiology predisposes patients to chronically low cardiac output, increased central venous pressure, and congestive heart failure. These altered hemodynamics lead to increased mesenteric vascular resistance, resulting in venous hypertension and congestion in protein-losing enteropathy. Plastic bronchitis is a complex disease in which chronic high lymphatic pressures from Fontan physiology cause acellular bronchial casts to develop. These entities may also occur in patients with normal Fontan hemodynamics. This article also covers medical and surgical interventions for protein-losing enteropathy and plastic bronchitis. (*Critical Care Nurse.* 2018;38[6]:e5-e12)

The Fontan procedure is the final stage of 3-stage palliation for patients with congenital heart disease and a functionally univentricular heart. The cardiovascular system does not achieve normal physiology with this repair but remains less efficient because of the lack of a pumping chamber to deliver blood to the lungs. Fontan physiology results in diminished cardiac output and increased systemic venous pressure. This physiology can lead to the life-threatening complications of protein-losing enteropathy (PLE) and plastic bronchitis (PB). Protein-losing enteropathy is characterized by dilation of lymphatic vessels (lymphangiectasis) resulting in hypoalbuminemia through intestinal protein loss. Plastic bronchitis is a disorder of the lymphatic system in which noninflammatory mucinous casts form in the tracheobronchial tree, causing significant obstruction of the bronchial airways.

 doi: https://doi.org/10.4037/ccn2018784

Protein-losing enteropathy is seen in approximately 3% to 10% of patients undergoing a Fontan procedure.[1] Plastic bronchitis is considered rarer, with less than 1% of Fontan patients developing this complication. However, in a recent study, a much higher prevalence of PB was reported by surveyed patients from a single institution.[2] Onset for either disease has a wide range, from as early as 1 month to 2 decades after the Fontan procedure. Different studies have reported onset occurring most commonly between 2 and 3 years following a Fontan procedure.[1-3] Survival at 5 years after diagnosis of PLE is 46%, and PB mortality rates range from 28% to 60% in patients with cyanotic heart disease or a previous Fontan procedure.[3,4] Why some patients develop PLE or PB but others with similar hemodynamics are spared is not evident.[5] Protein-losing enteropathy and PB remain significant complications despite surgical advances in intra- and extra-atrial Fontan repairs for patients with single-ventricle physiology. Both conditions continue to cause significant morbidity and mortality despite aggressive medical or surgical treatment upon diagnosis.

Risk factors that have been associated or correlated with PLE and PB include heterotaxy, anomalies of systemic venous drainage, increased pulmonary vascular resistance, longer cardiopulmonary bypass times, postoperative renal failure, and longer hospital stays.[2,3]

Patients with single-ventricle physiology undergoing Fontan procedure are at risk of protein-losing enteropathy and plastic bronchitis.

Although patients with PLE and PB often present with elevated pulmonary vascular resistance (PVR), those with PB can present without elevated PVR or increased right atrial pressure.[1] Fontan circulation itself is a risk factor for these conditions. In normal circulation, a subpulmonary chamber pumps blood to lungs with normal PVR and a subaortic chamber pumps blood to systemic vessels with normal systemic vascular resistance (SVR). In Fontan circulation, on the contrary, a single ventricle ejects against the impedance created by an abnormally elevated SVR, the mechanical impedance of the Fontan pathway itself, and the PVR (Figure 1).[6] The elevated SVR leads to increased afterload of the functional single ventricle. The elevated SVR in single-ventricle physiology also affects ventricular contractility. The result is a mismatch between ventricular contractility and afterload following the Fontan repair. This altered pathway leads to a chronic state of diminished cardiac output, high venous pressure, and dilation of lymphatic vessels.

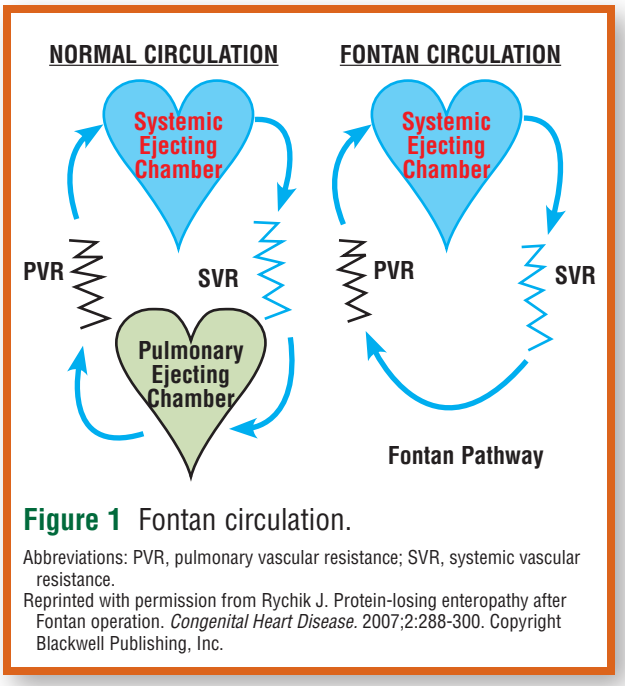

Figure 1 Fontan circulation.

Abbreviations: PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

Reprinted with permission from Rychik J. Protein-losing enteropathy after Fontan operation. *Congenital Heart Disease.* 2007;2:288-300. Copyright Blackwell Publishing, Inc.

Protein-Losing Enteropathy

Chronic low cardiac output from Fontan circulation and single-ventricle physiology may lead to mesenteric vasoconstriction. Rychik and Gui-Yang[7] studied the Doppler flow patterns in the superior mesenteric arteries of patients with normal physiology, patients with Fontan physiology without PLE, and patients with Fontan physiology and PLE. Patients with active PLE had absent diastolic flow, suggesting very high mesenteric vascular resistance. The author proposed a paradigm for the mechanism of PLE (Figure 2).[6] The low cardiac output, high venous pressure, and congestive heart failure in patients with Fontan physiology lead to increased mesenteric vascular resistance, resulting in venous hypertension and congestion. Congestive heart failure and

Author

Christine Peyton is a clinical nurse specialist at the Heart Institute at Children's Hospital Colorado, Aurora, Colorado.

Corresponding author: Christine Peyton, MS, CPNP-AC, CCRN, 13123 E. 16th Ave, Box 555, Aurora, CO 80045 (email: christine.peyton@childrencolorado.org).

To purchase electronic or print reprints, contact the American Association of Critical-Care Nurses, 101 Columbia, Aliso Viejo, CA 92656. Phone, (800) 899-1712 or (949) 362-2050 (ext 532); fax, (949) 362-2049; email, reprints@aacn.org.

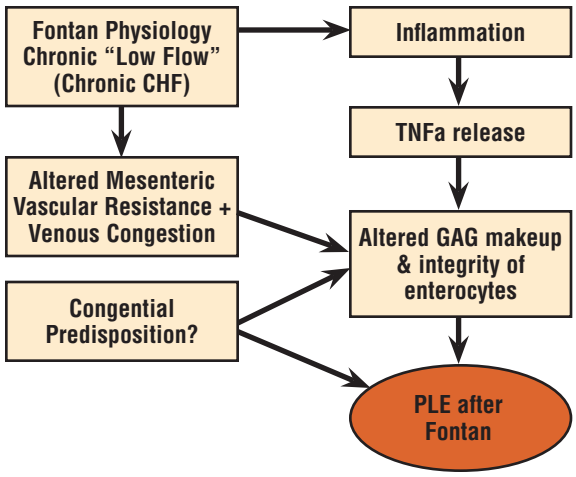

Figure 2 Proposed mechanism of protein-losing enteropathy.

Abbreviations: CHF, chronic heart failure; GAG, glycosaminoglycan; PLE, protein-losing enteropathy; TNFa, tumor necrosis factor α.
Reprinted with permission from Rychik J. Protein-losing enteropathy after Fontan operation. *Congenital Heart Disease.* 2007;2:288-300. Copyright Blackwell Publishing, Inc.

low cardiac output cause inflammation, which results in the release of tumor necrosis factor α, subsequently disrupting intestinal integrity and leading to protein leakage. The release of tumor necrosis factor α alters enterocyte basal membrane glycosaminoglycan makeup and basal membrane heparin sulfate, contributing to the existing protein leak. Patients may have an unknown congenital predisposition to protein leakage that may progress to a disease state when conditions of the Fontan pathway are present.[6] Meadows and colleagues[8] have extended the paradigm to consider PLE a disorder of lymphatic insufficiency. Their study found that central venous thrombosis and other forms of central venous obstruction may be contributive or causative factors of PLE. Thus, poor perfusion and dilated lymphatic vessels in combination with inflammation and a genetic predisposition are thought to be responsible for the development of PLE.[6,8] Protein-losing enteropathy is largely a disease of central venous congestion, so patients may have normal systolic function and cardiac output.

Clinical manifestations of PLE include abnormal lymphatic flow, hypoalbuminemia, and coagulopathies. Lymphangiectasia, a hallmark sign of PLE, is a result of increased SVR. Increased SVR causes lymphatic vessels to dilate, leading to loss of protein into the gut and hypoproteinemia. Loss of albumin reduces the transport capacity of calcium, causing hypocalcemia.[9] Adverse effects of hypocalcemia include osteopenia, poor growth, and (in severe cases) tetany. Protein loss and hypoalbuminemia can also predispose patients to hypogammaglobulinemia and loss of immunoglobulin G. Low serum protein decreases circulating coagulation factors because of deficiencies in basal membrane heparin caused by altered glycosaminoglycan makeup.[6] Loss of coagulation factors can produce a hypercoagulable state.[9] Excessive lymphatic fluid contributes to the engorged intestinal lymphatic system in PLE, resulting in lymphopenia and immunodeficiency.[9]

The gold standard for diagnosis of PLE is the 24-hour stool α_1-antitrypsin (AAT) clearance study.[9] α_1-Antitrypsin is a protein produced by the liver and excreted in the stool. The reference value for this study is less than 30 mL of AAT cleared in the stool in 24 hours. In patients with PLE, hundreds of milliliters of AAT are cleared in 24 hours. An increased spot concentration of fecal AAT is also diagnostic of PLE; however, a low concentration should not rule out PLE.[9] In patients with PLE, the serum albumin level is less than 2.5 g/dL. Patients with PLE become symptomatic because of protein loss and nutrient malabsorption. Symptoms of intestinal protein loss and lowered intravascular oncotic pressure include peripheral edema, pleural effusion, chylothorax, abdominal bloating, ascites, diarrhea, and failure to thrive. Magnetic resonance imaging in patients with single-ventricle Fontan physiology reveals lymphatic abnormalities including thoracic duct dilation, lymphangiectasia, and lymphatic collaterals.[10]

Protein-losing enteropathy and plastic bronchitis remain challenging diseases to treat despite advances in surgical and medical therapies.

Treatment strategies are directed toward altering the underlying cardiac hemodynamics, correcting hypoproteinemia, and improving protein homeostasis through nutritional support and protein replacement therapy (Table 1). Dietary interventions to promote protein homeostasis include increasing dietary protein and medium-chain triglycerides and reducing sodium and fat. Clinicians should monitor this diet's effect on the serum albumin level. Fluid restriction may also be indicated for patients with peripheral edema, fluid overload, and ascites. Adherence to dietary restrictions is a

Table 1 Medical treatments for protein-losing enteropathy

Intervention	Therapy	Mechanism of action
Dietary	High dietary protein and medium-chain triglycerides, low sodium and fat	Provides high calorie content to treat malnutrition Reduces intestinal lymphatic flow
	Fluid restriction	Decreases fluid overload and lowers central venous pressure; most effective in conjunction with diuretic therapy
Pharmacologic	Furosemide	Inhibits sodium, potassium, chloride, and water reabsorption in the loop of Henle, leading to fluid excretion and lower central venous pressure
	Spironolactone	Supplemental diuretic; prevents proteinuria
	Sildenafil	Decreases resistance in pulmonary bed and reduces systemic vascular resistance
	Budesonide	Corticosteroid; decreases inflammation with predominantly glucocorticoid action; has high first-pass metabolism in the liver so acts locally on intestines
	Heparin	Decreases inflammation by preventing mast cell degeneration in intestine; prevents thromboembolic events; acts as a barrier to large molecules like albumin
	Intravenous immunoglobulin	Increases albumin and immunoglobulin G levels; decreases edema
	Octreotide	Mimics natural somatostatin and decreases thoracic lymphatic drainage

concern because families often struggle to follow the rigid daily nutritional regimen. Albumin replacements are recommended when serum albumin levels fall below 2.5 g/dL; however, treatment should be aimed at controlling protein leakage that leads to hypoalbuminemia.[9] Frequent albumin replacements may be required for symptomatic relief if protein loss is not well controlled. Intravenous immunoglobulin replacements are useful to treat hypogammaglobulinemia associated with low immunoglobulin G levels and to increase serum albumin levels.[11]

Pharmaceutical therapy options are patient specific (Table 1). Diuretics and pulmonary vasodilators can decrease central venous pressure and optimize cardiac output. Diuretics may be used to alleviate peripheral edema and fluid overload. Pulmonary vasodilators such as sildenafil citrate have been found to decrease PVR in the pulmonary bed and reduce SVR to optimize the Fontan circulation. Inflammation caused by congestive heart failure can be controlled with corticosteroids and heparin sulfate.

Treatment for protein-losing enteropathy and plastic bronchitis are aimed at controlling symptoms and improving patients' quality of life.

Corticosteroids and heparin sulfate can decrease inflammation by targeting intestinal mucosa and reducing enteric protein losses. Oral budesonide, a potent synthetic glucocorticoid that is delivered primarily to the small intestine, is effective in some patients.[12] Systemic absorption of budesonide can lead to adrenal suppression and verruca vulgaris. My clinical experience has shown that symptoms are likely to return when the patient is weaned off corticosteroids. In addition to preventing thromboembolic events, heparin may decrease inflammation by inhibiting mast cell degeneration in the intestine. Octreotide mimics somatostatin and may decrease thoracic duct lymphatic drainage associated with chylothorax and lymphangiectasia.[13] Heparin and octreotide are not primary treatments for PLE but are used to treat patients with refractory PLE.[13]

Fontan fenestration may be performed in the cardiac catheterization laboratory to relieve pressure due to obstruction within the systemic venous to pulmonary artery pathway (Table 2). The fenestration allows desaturated blood to shunt to the atrial cavity, providing additional preload to the systemic ventricle and increasing cardiac output and ventricular filling.[14] The increase in cardiac output also improves overall central venous congestion. Arterial desaturation should be anticipated

Table 2 Interventional and surgical treatments for protein-losing enteropathy (PLE)

Intervention	Therapy	Advantages	Disadvantages
Interventional catheterization	Fontan fenestration	Reduces systemic vascular resistance and improves cardiac output	Systemic arterial blood oxygen desaturation Spontaneous closure or occlusion following procedure
Electrophysiology procedure	Epicardial pacing	Restores atrioventricular synchrony	Pacer dysfunction, maintenance
Surgical intervention	Fontan revision: conversion from atriopulmonary connection to total cavopulmonary artery connection	Relieves mechanical pathway obstruction; controls atrial arrhythmias Increases cardiac output and decreases venous congestion	Complex operation with high mortality Reoccurrence of PLE symptoms
	Heart transplant	Initially resolves PLE symptoms	Reoccurrence of PLE is common Lifelong antirejection medications Organ rejection, coronary artery disease

following a fenestration; however, overall tissue delivery improves. Indications for fenestration are acute postoperative hemodynamic deterioration, chronic pleural effusion, and exercise intolerance.[14] If PLE symptoms occur following a fenestration, a spontaneous closure of the fenestration or occlusion should be suspected. Atrial pacing can be considered for PLE treatment in patients who have lost sinus node function or experienced a junctional rhythm following the Fontan procedure. Atrial pacing can correct cardiac hemodynamic instability by restoring atrioventricular synchrony and maximizing cardiac output.

Surgical intervention with a Fontan revision or heart transplant may be indicated in patients with refractory or recurrent conditions. Fontan revision is usually required for patients who receive an atriopulmonary connection because this classical surgical repair can lead to low cardiac output, thrombi, and refractory atrial tachyarrhythmias.[15] When intervention is indicated, the atriopulmonary connection is surgically revised to an extracardiac circulation. Historically, mortality has been as high as 50% in patients with PLE undergoing Fontan conversion.[15,16] Heart transplant is a consideration for patients with severe PLE whose condition is stable and refractory to medical and other surgical interventions.[17] The resolution of symptoms may take several months following heart transplant.[17] Patients with PLE are not ideal transplant candidates because they have poor nutrition, elevated antibody titers, multiple prior operations, increased risk of infection because of immunodeficiency, and single-ventricle physiology. Chronic malnutrition combined with asplenia may increase the risk of immunodeficiency and lead to more infections after transplant. Sensitization is more common in patients with repaired congenital heart disease, but detecting antibodies may be difficult because they are lost in the intestine. Standard testing for sensitization may result in a false-negative result, which then becomes a problem after transplant.

Plastic Bronchitis

Plastic bronchitis is a complex disease in which bronchial casts form in the airway and throughout the tracheobronchial tree. Casts can be classified as inflammatory or acellular. Inflammatory casts are composed mainly of fibrin and cellular infiltrates, and acellular casts are composed mainly of mucin and fibrin.[18] Plastic bronchitis following the Fontan procedure is usually associated with acellular casts, which result in serious pulmonary obstruction and possible death.[18] Hence, PB can present as a more acute, life-threatening disease than PLE.

Plastic bronchitis is thought to have a pathway similar to that of PLE. Altered hemodynamics consist of declining ventricular function with high central venous pressure due to the Fontan pathway, as described by Rychik.[6,9] Chronic high lymphatic pressures from Fontan physiology lead to the development of acellular bronchial casts, although some patients with Fontan physiology have both acellular and inflammatory casts. The acellular casts produce large, rubbery plugs of mucous and fibrin in the tracheobronchial airway. Intrathoracic

Table 3 Treatments for plastic bronchitis

Intervention	Therapy	Mechanisms of action
Dietary	High dietary protein, low fat	Provides high calorie content to treat malnutrition Reduces intestinal lymphatic flow
Pharmacological	Macrolide: azithromycin	Has anti-inflammatory and mucoregulatory effects
	Corticosteroid	Decreases bronchopulmonary inflammation
	Nebulized acetylcysteine	Mucus-thinning agent; assists with expectoration of bronchial casts
	Aerosolized tissue plasminogen activator	Dissolves bronchial casts in airways
	Aerosolized heparin	Has anti-inflammatory effect; decreases mucin secretion from bronchial casts
Surgical/ interventional catheterization	Thoracic duct ligation or coil embolization	Relieves congestion of lymphatic system and chronic chyle leak
	Heart transplant	Used to treat refractory plastic bronchitis not responding to medical treatment
Bronchoscopic	Flexible bronchoscopy	Removes casts by bronchial wash or forceps
Mechanical assist support	Extracorporeal membrane oxygenation	Provides cardiopulmonary support following cardiac arrest from airway obstruction by bronchial cast

pressures increase with cast development, resulting in interstitial pulmonary edema or lymphedema. The leakage of fluid into the thorax or pericardium leads to pericardial effusion and/or chylothorax. Surgical damage of the thoracic duct predisposes a patient to PB because of abnormalities in excessive production or drainage of lymphatic fluid.[19] Risk factors for PB are prolonged duration of chest tube drainage after surgery, chylothorax, and development of significant cardiopulmonary collateral vessels.[19]

Lymphatic insufficiency and excessive lymphatic fluid may cause lymphopenia and immunodeficiency. Lymphangiectasia is present in patients with PB; however, small amounts of protein are lost into the airway, not the gut as in PLE.[8] Hypoalbuminemia and hypogammaglobulinemia may be present in PB, but the dominant clinical manifestation is respiratory distress related to obstruction in the airway.

Symptoms in patients with PB include decreased breath sounds and airway obstruction due to bronchial hypersecretions. Patients with substantial airway obstruction from bronchial casts have coughing, shortness of breath, wheezing, and chest pain, and they may expectorate casts. Diagnosis of PB is confirmed by a history of expectoration of bronchial casts.[20] Bronchoscopy should be performed in patients with suspected PB who have dyspnea or signs of respiratory distress without expectoration of bronchial casts. Bronchoscopy also allows removal of casts during the diagnostic procedure. However, acellular casts tend to be friable and can be difficult to remove with bronchoscopy because the casts tend to adhere to the bronchial airways. High-resolution computed tomography shows patchy atelectasis of the involved bronchial airway and pulmonary segments.[20]

Treatments for PB include dietary, pharmacological, surgical interventions and interventional catheterization (Table 3). The dietary modification is a high-protein, low-fat diet. Mucus-thinning agents such as nebulized acetylcysteine may help treat bronchial casts. A bronchoscopy regimen may promote airway clearance of bronchial casts when using mucus-thinning agents and chest physiotherapy. Airway clearance using standard pulmonary toileting techniques and a high-frequency chest compression vest seems to be the safest and most effective treatment.[21] Pharmacologic treatment can be optimized with pulmonary vasodilators, aerosolized fibrinolytics, mucolytics, and inhaled steroids.[20] Budesonide and sildenafil citrate may be used in combination; their mechanism of action is the same as in treatment of PLE.[6,9,22] Oral budesonide may not be as effective for PB as for PLE because protein leakage occurs in the lungs and not the intestines. Aerosolized tissue plasminogen activator has also been used with some success to dissolve bronchial casts so they may be eliminated or more easily expectorated.[4,23] A combination of sildenafil citrate (a potent pulmonary vasodilator) and aerosolized tissue plasminogen activator to help lyse acellular casts is an effective treatment.[21,22] However, this therapy is associated with a risk of airway hemorrhage.

Aerosolized heparin has recently been shown to have anti-inflammatory properties that can decrease mucin secretion and prevent activation of the fibrin pathway for treatment of acellular casts.[21] In addition to their mucoregulatory effect, macrolides are thought to have an anti-inflammatory effect through modulation of inflammatory cytokines.[24]

Percutaneous thoracic duct coil embolization or thoracic duct ligation may be a treatment option for chronic chyle leakage and inflammation, although bronchial casts may redevelop after either procedure.[25] Heart transplant should be considered a treatment option for unresolved PB that has not responded to medical treatment. Several studies have reported long-term survival following heart transplant in patients with PB.[26,27] One institution reported 2 patients who are long-term survivors of heart transplant after failure of the Fontan procedure and development of PB.[26] Gossett et al[27] reported a 70% survival rate with no reoccurrence of bronchial casts following transplant.

Nursing Considerations

Protein-losing enteropathy fits into 3 treatment categories based on the patient's serum albumin level. Albumin levels of 2.5 to 3.5 g/dL are considered mild disease.[9] Albumin levels of 2.0 to 2.5 g/dL indicate moderate PLE, and levels less than 2.0 g/dL indicate severe PLE (Table 4).[9] A nurse caring for a patient with PLE should be aware of disease severity and anticipate interventions based on severity. Patients with serum albumin levels less than 2.5 g/dL may require frequent albumin replacements, but control of protein leakage is essential to prevent further hypoproteinemia. Infusion centers that provide albumin replacements can help prevent frequent hospitalizations. Central catheter duration and placement should be carefully considered in patients with signs of PLE because thrombosis from a central catheter can worsen the symptoms.[8] Patients may benefit from a peripherally inserted central catheter to allow for outpatient replacement therapy at infusion centers or at home. Families need to be taught meticulous central catheter care to prevent infection and avoid unnecessary hospitalization for central catheter–associated infections. Teaching families the importance of dietary modification can improve adherence to fluid restriction and the low-fat, high-protein diet. Adherence to dietary modifications may also prevent frequent hospitalizations.

Table 4 Protein-losing enteropathy (PLE) classification and therapy according to serum albumin level

Classification of PLE	Serum albumin, g/dL	Albumin replacement therapy
Mild	2.5-3.5	Recommend against albumin infusions
Moderate	2.0-2.5	Consider intermittent albumin infusions
Severe	<2.0	Strongly consider intermittent albumin infusions

Pulmonary toileting and chest physiotherapy should be regularly scheduled for patients with PB. The presentation of PB is similar to that of foreign body aspiration. Acute changes in ventilator capacity can lead to tachypnea and increased intrapulmonary pressures. Acute interstitial pulmonary edema and respiratory failure may result in rapid decompensation and possible cardiopulmonary failure. Nurses may need to respond quickly to decompensation and initiate cardiopulmonary resuscitation in patients with PB. The interdisciplinary team should prepare the patient and family for mechanical assist device therapy such as extracorporeal membrane oxygenation.

Symptoms of PLE and PB may be controlled well with individualized medical treatment, but patients with these conditions may have frequent exacerbations. These exacerbations can lead to frequent readmissions, so patients and families may need psychosocial support because of the chronic nature of these diseases. Palliative care should be considered for all PLE and PB patients because the trial-and-error approach to treatment can affect quality of life. Interdisciplinary care should focus on minimizing symptoms, decreasing hospitalizations, and maximizing quality of life. Care teams should include nurses, social workers, child life specialists, dieticians, and psychologists to support families' psychosocial needs. Formal discharge education to reinforce medical treatments and diet can improve adherence among patients and families. Patients and families can also benefit from structured care coordination to promote successful discharge to home.

Conclusion

Protein-losing enteropathy and PB after Fontan repair are challenging to treat despite advances in surgical and medical therapy. Recently proposed paradigms provide

guidelines to better understand PLE and PB disease processes. Patients with PLE and PB can be treated with a wide variety of medical and surgical options; however, individual patient response remains a challenge. Clinical pathways need to be established and tested with randomized multicenter clinical trials or quality improvement collaboratives. Protein-losing enteropathy and PB are chronic diseases that expose patients and families to many psychosocial stressors. Treatments for both diseases are aimed at controlling symptoms and improving quality of life. CCN

Acknowledgments
The author would like to thank Jack Rychik, MD, for his contributions to research and the development of a paradigm for protein-losing enteropathy and plastic bronchitis.

Financial Disclosures
None reported.

References

1. Merten L, Hagler DJ, Sauer U, Somerville J, Gewillig M. Protein-losing enteropathy after the Fontan operation: an international multicenter study. PLE study group. *J Thorac Cardiovasc Surg.* 1998;115(5):1063-1073.
2. Caruthers RL, Kempa M, Loo A, et al. Demographic characteristics and estimated prevalence of Fontan-associated plastic bronchitis. *Pediatr Cardiol.* 2013;34(2):256-261.
3. Feldt RH, Driscoll DJ, Offord KP, et al. Protein-losing enteropathy after the Fontan operation. *J Thorac Cardiovasc Surg.* 1996;112(3):672-680.
4. Gibb E, Blount R, Lewis N, et al. Management of plastic bronchitis with topical tissue-type plasminogen activator. *Pediatrics.* 2012;130(2):e446-e450.
5. Gewillig M, Goldberg DJ. Failure of the fontan circulation. *Heart Fail Clin.* 2014;10(1):105-116.
6. Rychik J. Protein-losing enteropathy after Fontan operation. *Congenit Heart Dis.* 2007;2(5):288-300.
7. Rychik J, Gui-Yang S. Relation of mesenteric vascular resistance after Fontan operation and protein-losing enteropathy. *Am J Cardiol.* 2002; 90(6):672-674.
8. Meadows J, Jenkins K. Protein losing enteropathy: integrating a new disease paradigm into recommendations for prevention and treatment. *Cardiol Young.* 2011;21(4):363-377.
9. Goldberg DJ, Dodds K, Rychik J. Rare problems associated with the Fontan circulation. *Cardiol Young.* 2010;20(suppl 3):113-119.
10. Dori Y, Keller MS, Fogel MA, et al. MRI of lymphatic abnormalities after functional single-ventricle palliation surgery. *AJR Am J Roentgenol.* 2014;203(2):426-431.
11. Zaupper LB, Nielsen BW, Herlin T. Protein-losing enteropathy after the total cavopulmonary connection: impact of intravenous immunoglobulin. *Congenit Heart Dis.* 2011;6(6):624-629.
12. Turner Z, Lanford L, Webber S. Oral budesonide as a therapy for protein-losing enteropathy in patients having undergone Fontan palliation. *Congenit Heart Dis.* 2012;7(1):24-30.
13. John AS, Phillips SD, Driscoll DJ, Warnes CA, Cetta F. The use of octreotide to successfully treat protein-losing enteropathy following the Fontan operation. *Congenit Heart Dis.* 2011;6(6):653-656.
14. Vyas H, Driscoll DJ, Cabalka AK, Cetta F, Hagler DJ. Results of transcatheter Fontan fenestration to treat protein losing enteropathy. *Catheter Cardiovasc Interv.* 2007;69(4):584-589.
15. Sheikh AM, Tang AT, Roman K, et al. The failing Fontan circulation: successful conversion of atriopulmonary connections. *J Thorac Cardiovasc Surg.* 2004;128(1):60-66.
16. Jang WS, Kim WH, Choi K, et al. The mid-term surgical results of Fontan conversion with antiarrhythmia surgery. *Eur J Cardiothorac Surg.* 2014; 45(5):922-927.
17. Jayakumar KA, Addonizio LJ, Kichuk-Chrisant MR, et al. Cardiac transplantation after the Fontan or Glenn procedure. *J Am Coll Cardiol.* 2004; 44(10):2065-2072.
18. Larue M, Gossett JG, Stewart RD, Backer CL, Mavroudis C, Jacobs ML. Plastic bronchitis in patients with fontan physiology: review of the literature and preliminary experience with fontan conversion and cardiac transplantation. *World J Pediatr Congenit Heart Surg.* 2012;3(3): 364-372.
19. Schumacher KR, Singh TP, Kuebler J, Aprile K, O'Brien M, Blume ED. Risk factors and outcome of Fontan-associated plastic bronchitis: a case-control study. *J Am Heart Assoc.* 2014;3(2):e000865.
20. Grutter G, Di Carlo D, Gandolfo F, et al. Plastic bronchitis after extracardiac Fontan operation. *Ann Thorac Surg.* 2012;94(3):860-864.
21. Rubin BK. Plastic bronchitis. *Clin Chest Med.* 2016;37(3):405-408.
22. Goldberg DJ, Shaddy RE, Ravishankar C, Rychik J. The failing Fontan: etiology, diagnosis and management. *Expert Rev Cardiovasc Ther.* 2011; 9(6):785-793.
23. Costello JM, Steinhorn D, McColley S, Gerber ME, Kumar SP. Treatment of plastic bronchitis in a Fontan patient with tissue plasminogen activator: a case report and review of the literature. *Pediatrics.* 2002;109(4):e67.
24. Shinkai M, Rubin BK. Macrolides and airway inflammation in children. *Paediatr Respir Rev.* 2005;6(3):227-235.
25. Languepin J, Scheinmann P, Mahut B, et al. Bronchial casts in children with cardiopathies: the role of pulmonary lymphatic abnormalities. *Pediatr Pulmonol.* 1999;28(5):329-336.
26. Backer CL, Russell HM, Pahl E, et al. Heart transplantation for the failing Fontan. *Ann Thorac Surg.* 2013;96(4):1413-1419.
27. Gossett JG, Almond CS, Kirk R, et al. Outcomes of cardiac transplantation in single-ventricle patients with plastic bronchitis: a multicenter study. *J Am Coll Cardiol.* 2013;61(9):985-986.