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Clinical Outcomes and Improved Survival in Patients With Protein-Losing Enteropathy After the Fontan Operation

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ABSTRACT

BACKGROUND Patients with protein-losing enteropathy (PLE) following the Fontan operation have a reported 50% mortality at 5 years after diagnosis.

OBJECTIVES The aim of this study was to review outcomes in patients with PLE following the Fontan operation.

METHODS From 1992 to 2010, 42 patients (55% male) with PLE following the Fontan operation were identified from clinical databases at the Mayo Clinic. Data were collected retrospectively.

RESULTS Mean age at PLE diagnosis was 18.9 ± 11.0 years. Initial Fontan operation was performed at 10.1 ± 10.8 years of age. Mean time from Fontan operation to PLE diagnosis was 8.4 ± 14.2 years. Survival was 88% at 5 years. Decreased survival was seen in patients with high Fontan pressure (mean >15 mm Hg; $p = 0.04$), decreased ventricular function (ejection fraction <55%; $p = 0.03$), and New York Heart Association functional class >2 at diagnosis ($p = 0.04$). Patients who died had higher pulmonary vascular resistance (3.8 ± 1.6 Wood units [WU] vs. 2.1 ± 1.1 WU; $p = 0.017$), lower cardiac index (1.6 ± 0.4 l/min/m^2 vs. 2.7 ± 0.7 l/min/m^2; $p < 0.0001$), and lower mixed venous saturation (53% vs. 66%; $p = 0.01$), compared with survivors. Factors were assessed at the time of PLE diagnosis. Treatments used more frequently in survivors with PLE included spironolactone (21 [68%]), octreotide (7 [21%]), sildenafil (6 [19%]), fenestration creation (15 [48%]), and relief of Fontan obstruction (7 [23%]).

CONCLUSIONS PLE remains difficult to treat; however, in the current era, survival has improved with advances in treatment. Further study is needed to better understand the mechanism of disease and ideal treatment strategy.
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Protein-losing enteropathy (PLE) occurs in 5% to 15% of patients after the modified Fontan operation and has been a historically difficult complication to treat (1,2). PLE is characterized by the enteric loss of proteins such as albumin, immunoglobulins, and clotting factors. The protein loss that occurs leads to the clinical findings of peripheral edema, ascites, diarrhea, weight loss, and malabsorption. The exact mechanisms of this complication are poorly understood, and treatment strategies vary.

Patients with PLE following the Fontan operation have a reported 50% mortality at 5 years after initial diagnosis (1,2). Numerous treatment strategies have been used, including medical therapy, such as controlled-release budesonide and sildenafil, as well as interventional and surgical therapies, such as Fontan revision and Fontan fenestration creation (3–6). Even with these treatment advances, limited studies have reported improved survival

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for patients with PLE following the Fontan operation (7).

The purpose of this study was to determine the survival of patients with PLE following the Fontan operation in the current era. We sought to identify factors associated with patient mortality and to review treatment strategies used in survivors.

METHODS

Patients with PLE following the Fontan operation who were seen at the Mayo Clinic between 1992 and 2010 were identified from clinical databases. Of the 42 patients identified, 25 (60%) had their original Fontan operation performed at the Mayo Clinic, whereas 17 (40%) had their original Fontan operation performed elsewhere. Data were collected by retrospective chart review. Surgical details, treatment course, and response to treatment as assessed by laboratory assessment and clinical improvement were recorded. Echocardiograms and cardiac catheterization data were reviewed for the presence of valvular regurgitation, ventricular function (estimated ejection fraction [EF]), cardiac output, pulmonary vascular resistance, and intracardiac pressures, including ventricular end-diastolic pressure. Cardiac catheterization data were obtained within 2 years following diagnosis in most patients. For 5 patients, data were obtained from catheterizations 3 to 5 years following diagnosis. Fontan pressures were measured in the Fontan pathway. In cases of Fontan obstruction, pressures following relief of obstruction were recorded. Serum albumin levels, total protein levels, and fecal alpha 1 antitrypsin clearance at diagnosis were recorded. Survival was ascertained through medical record review and confirmed through Accurint (LexisNexis, New York, New York). The protocol was approved by the Mayo Clinic Foundation's institutional review board (Protocol 10-004994).

Patients in this cohort presented with clinical symptoms or decreased serum albumin levels. The diagnosis of PLE was made through a combination of clinical symptoms (peripheral edema, diarrhea, abdominal pain, or effusions within the pericardial or pleural space), elevated fecal alpha-1 antitrypsin clearance (>50 ml/24 h or elevated spot fecal alpha 1 antitrypsin concentration [>100 mg/ml]), and serum albumin <3.0 g/dl. The presence of 1 clinical feature with both laboratory abnormalities was needed for diagnosis. Patients with other primary causes of hypoproteinemia, such as nephrotic syndrome or intestinal lymphangiectasia (n = 1), were excluded as were patients with known inflammatory bowel disease, such as Crohn's disease or ulcerative colitis.

ABBREVIATIONS AND ACRONYMS

EF = ejection fraction

NYHA = New York Heart Association

PLE = protein-losing enteropathy

STATISTICAL ANALYSIS. Continuous variables are expressed as mean ± SD or median (interquartile range) when appropriate. Differences in median age and time intervals from surgery were examined using the Wilcoxon rank-sum test. Frequencies with proportions were determined for categorical variables. Survival curves were generated through Kaplan-Meier analysis and compared using log-rank tests. Laboratory and hemodynamic variables were further analyzed through the chi-square test. The Fisher exact test was used when appropriate to account for small sample size distribution. Due to the small sample size, variables were examined through a univariate analysis only. All statistical analyses were conducted using SAS version 9.2 (SAS Institute, Cary, North Carolina).

RESULTS

PATIENT DEMOGRAPHICS. Forty-two patients with PLE following a Fontan operation were identified. Patient demographics are summarized in Table 1. The mean time from diagnosis to last follow-up was 8.4 ± 6 years (range 1 to 22 years). Mean age at follow-up was 26.5 ± 11.6 years (range 5 to 58 years). Underlying cardiac anatomy was tricuspid atresia in 12 patients (29%), double inlet left ventricle in 11 patients (26%), unbalanced atrioventricular septal defect in 7 patients (17%), pulmonary atresia with intact ventricular septum in 4 patients (10%), mitral atresia with double outlet right ventricle in 3 patients (7%), mitral atresia in 2 patients (5%), hypoplastic left heart syndrome in 1 patient (2%), Shone syndrome in 1 patient (2%), and L-transposition of the great arteries with straddling left atrioventricular valve in 1 patient (2%). The predominant morphology was left ventricular in 27 patients (64%).

SURGICAL HISTORY. All patients had surgical procedures before the Fontan operation. There was no association between the number or type of prior surgical procedures and decreased survival in patients diagnosed with PLE after the Fontan operation. Initial Fontan operations were performed between 1974 and 2005; one-half of this cohort underwent surgery after 1990. Nine patients had surgery before 1985. Six of the 11 patients who died had their initial Fontan operation before 1985. Two patients had atrioventricular valve replacements before PLE diagnosis, due to severe valve regurgitation. Six patients had fenestrations placed at the initial Fontan operation. One patient had a Fontan fenestration created in the cardiac catheterization laboratory 1 month after

TABLE 1 Demographics

	Alive (n = 31)	Deceased (n = 11)	p Value	Total Cohort (N = 42)
Median age at PLE diagnosis, yrs	14 (4.7-57)	22 (12-39)	0.01	17 (4.7-57)
Median age at Fontan operation, yrs	8 (2-38)	11.9 (2-37)	NS	8.3 (2-38)
Median time: Fontan operation to PLE, yrs	6.5 (1-27)	10.4 (1-20)	NS	7.8 (1-27)
Male	16 (52)	7 (64)	NS	23 (55)
Type of initial Fontan operation			NS	
Atriopulmonary connections	19 (61)	9 (81)		28 (67)
Lateral tunnel or intra-atrial conduit	4 (13)	2 (19)		6 (14)
Extracardiac conduit	8 (26)	0		8 (19)
Predominant ventricular morphology			NS	
Left	19 (61)	8 (73)		27 (64)
Right	12 (39)	3 (27)		15 (36)

Values are mean (range) or n (%).
NS = not significant; PLE = protein-losing enteropathy.

the Fontan operation, due to recurrent pleural effusions. Two patients had patent fenestrations at the time of PLE diagnosis.

PATIENT SURVIVAL. Survival was 88% at 5 years after diagnosis of PLE (Fig. 1). There were 11 deaths. Mean age at death was 32 ± 7.7 years of age (range 22 to 47 years). Mean time interval from diagnosis to death was 7.5 ± 5.4 years (range 1 to 18 years). Causes of death included sepsis (n = 7), complications after Fontan conversion (n = 1), and unknown (n = 3).

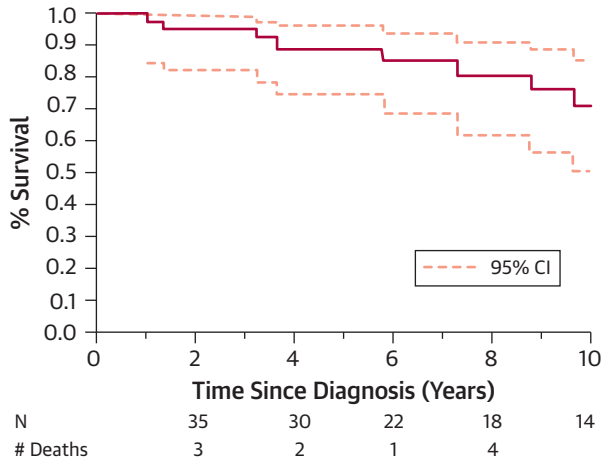


FIGURE 1 Survival Curve for Patients With PLE After the Fontan Operation

Survival in this patient cohort was 88% at 5 years after protein-losing enteropathy PLE diagnosis.

Factors associated with decreased survival included high Fontan pressure (mean >15 mm Hg; p = 0.04), decreased ventricular function (estimated EF <55%; p = 0.01), and New York Heart Association (NYHA) functional class >II (p = 0.03) at diagnosis (Fig. 2). Patients with Fontan pressures >15 mm Hg at the time of diagnosis of PLE had 5- and 10-year survival rates of 83% and 63%, respectively. In contrast, patients with Fontan pressures <15 mm Hg had 5- and 10-year survival rates of 95% and 86%, respectively. Similarly, patients with estimated EF of <55% had 5- and 10-year survival rates of 87% and 62%, compared with 91% and 85% in patients with EF >55%. NYHA functional class III or IV at time of diagnosis was associated with decreased 5- and 10-year survival, with rates of 83% and 45% versus 95% at both 5 and 10 years in patients with NYHA functional class I or II.

Patients who died had higher pulmonary vascular resistance (3.8 ± 1.6 Wood units [WU] vs. 2.1 ± 1.1 WU; p = 0.017), lower cardiac index (1.6 ± 0.4 l/min/m^2 vs. 2.7 ± 0.7 l/min/m^2; p < 0.0001), and lower mixed venous oxygen saturation (53% vs. 66%; p = 0.01), compared with survivors (Table 2). Laboratory assessment revealed that serum creatinine levels were significantly higher in patients who died compared with those in survivors (1.34 ± 0.40 mg/dl vs. 0.84 ± 0.33 mg/dl; p = 0.03). Ventricular end-diastolic pressure, serum hemoglobin levels, serum albumin levels, and fecal alpha 1 antitrypsin levels were not significantly different in survivors versus nonsurvivors (Table 2).

Atrial tachyarrhythmias were present in 28 patients (67%). Patients with atrial arrhythmias had decreased survival at both 5 and 10 years, although the differences were not statistically significant (p = 0.07) (Fig. 2D). Therapies to control arrhythmias included radiofrequency ablation in 23 patients, antiarrhythmic medications in 28 patients, pacemaker therapy in 17 patients, and Fontan conversion in 9 patients.

MEDICAL AND SURGICAL THERAPY. Medical therapy only (n = 15) resulted in symptomatic improvement in 7 patients (47%), no improvement in 5 (33%), and death in 3 (20%). Medical plus surgical/interventional procedures (n = 27) resulted in symptomatic improvement in 10 patients (37%), no improvement in 9 (33%), and death in 8 (30%). Types of therapies used are described in Table 3. Medical therapies used more frequently in survivors versus nonsurvivors included spironolactone, octreotide, and sildenafil. Surgical therapies used more frequently in survivors included fenestration placement and relief of obstruction within the Fontan pathway.

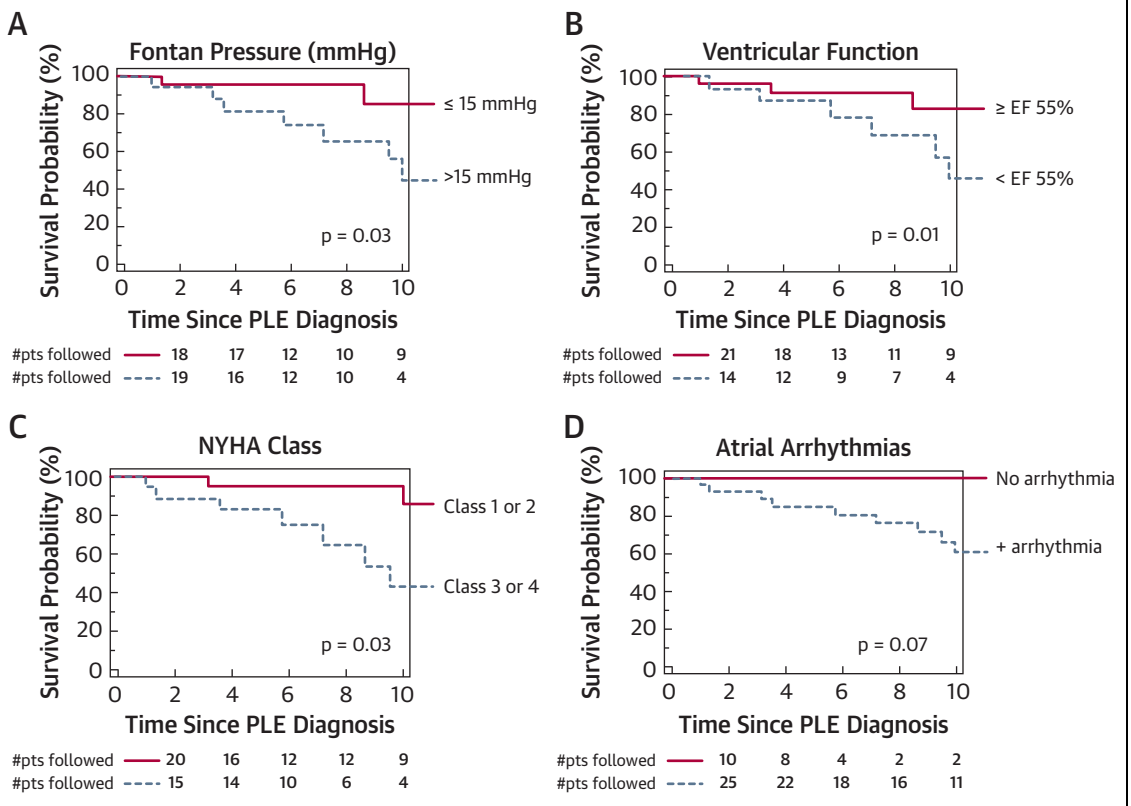


FIGURE 2 Factors Affecting Survival in Patients With PLE After the Fontan Operation

Fontan pressure <15 mm Hg **(A)**, ventricular function >55% **(B)**, and New York Heart Association (NYHA) functional class III or IV **(C)** at time of diagnosis were associated with decreased survival. The presence of atrial arrhythmias **(D)** was also associated with decreased survival, although this association was not statistically significant. EF = ejection fraction; other abbreviation as in Figure 1.

In addition to the medical therapies described, intravenous immunoglobulin therapy was used in 3 patients and infliximab was used in 1 patient.

TABLE 2 Laboratory and Hemodynamic Assessments at Time of PLE Diagnosis

	Alive (n = 31)	Deceased (n = 11)	p Value
PVR, WU	2.1 ± 1.1	3.6 ± 1.6	0.017
Cardiac index, l/min/m^2	2.7 ± 0.7	1.6 ± 0.4	0.02
Mixed venous saturation, %	66.0 ± 8.1	53.0 ± 7.8	0.01
Creatinine, mg/dl	0.84 ± 0.33	1.34 ± 0.4	0.03
Albumin, mg/dl	2.5 ± 0.6	2.4 ± 0.6	NS
Stool alpha 1 antitrypsin, mg/dl	321 ± 179	371 ± 138	NS
Hemoglobin, mg/dl	14.0 ± 3.3	13.0 ± 1.8	NS
Ventricular end-diastolic pressure, mm Hg	11 ± 3	10 ± 2	NS

Values are mean ± SD.

PVR = pulmonary vascular resistance; WU = Wood units; other abbreviations as in Table 1.

Intravenous diuretic agents with or without albumin therapy were used in 37 patients (90%), primarily during symptomatic periods. Mean albumin level at time of follow-up was 3.3 ± 0.96 mg/dl. Additional surgical therapies included Fontan takedown in 2 patients; 1 had symptomatic relief, whereas the other remained with PLE-related symptoms. One patient had additional coiling of venovenous collateral. Cardiac valve repair, closure, or replacement was used in 4 patients who had severe valve regurgitation. Cardiac transplantation was performed in 1 patient at the time of this review, and it resulted in resolution of PLE.

DISCUSSION

PLE after the Fontan operation remains a difficult complication to treat. Historically, survival following diagnosis has been dismal, with mortality rates of 50% at 5 years after diagnosis (1,2). The purpose

TABLE 3 Medical and Surgical Treatment Strategies for PLE After Fontan Operation

	Alive (n = 31)	Deceased (n = 11)	Total Cohort (N = 42)
Medical therapies			
Heparin	14 (45)	7 (63)	21 (50)
Loop diuretics	25 (81)	10 (91)	35 (83)
Low-fat diet, MCT oil	17 (55)	11 (100)	28 (67)
ACE inhibitors, ARB	23 (74)	9 (81)	32 (76)
Spironolactone	21 (67)	5 (45)	26 (62)
Antiarrhythmic medications	10 (32)	5 (45)	15 (36)
Octreotide	7 (23)	1 (9)	8 (19)
Iron ± transfusion	4 (13)	6 (55)	10 (24)
Sildenafil	6 (19)	1 (9)	7 (17)
Steroids	9 (29)	3 (27)	12 (29)
Surgical/interventional therapies			
Fontan fenestration	16 (52)	5 (45)	21 (50)
Fontan conversion*	7 (23)	2 (18)	9 (21)
Fontan obstruction relief	7 (23)	2 (18)	9 (21)
Ablation therapy	15 (48)	8 (73)	23 (55)
Valve replacement, repair, or closure	3 (10)	1 (9)	4 (10)

Values are n (%). *Performed for atrial arrhythmias (7 cases) and obstruction (2 cases).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; MCT = medium chain triglycerides; other abbreviation as in Table 1.

of our study was to examine the survival rate of patients with PLE following the Fontan operation in the current era. In addition, we identified factors that are associated with decreased survival and described current treatment strategies for patients with PLE following the Fontan operation (**Central Illustration**). Because all patients had PLE, no conclusions can be made from this study about the risk factors for the development of PLE.

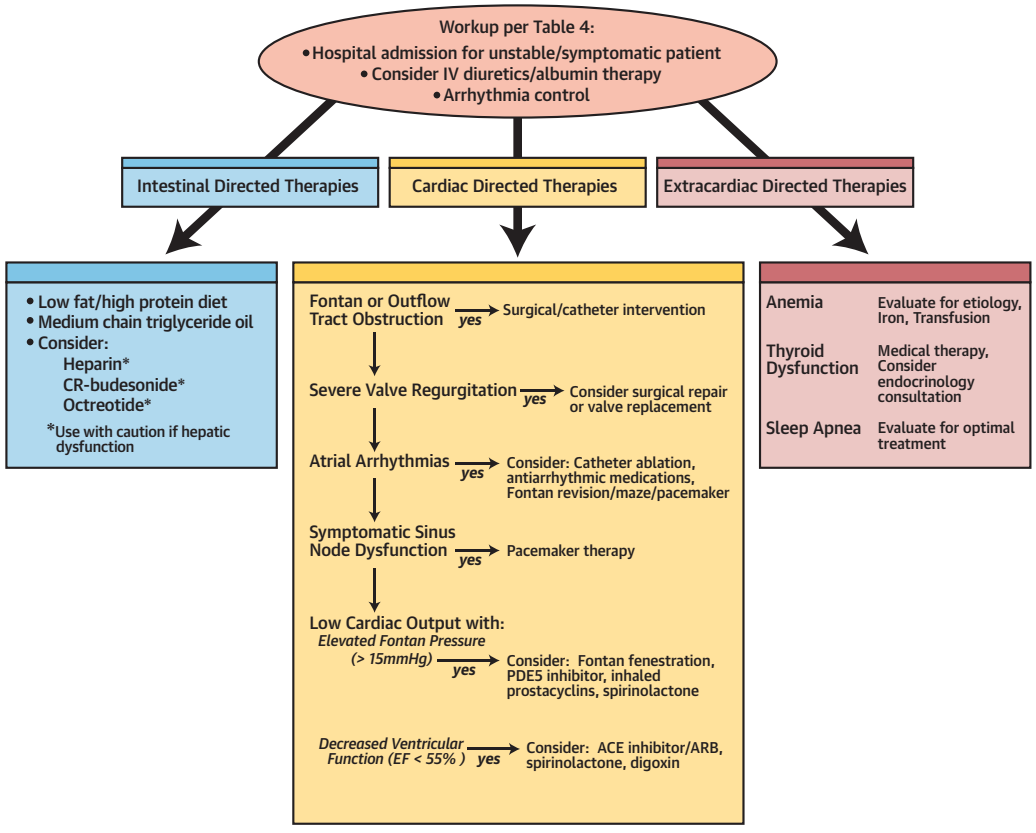
Survival in our cohort was markedly improved from previous reports. Patients had an 88% and 72% survival rate at 5 and 10 years, respectively, after PLE diagnosis. Recent single-center studies have reported similar findings of improved survival after diagnosis with PLE (7). These improved survival rates may be partly due to improved survival rates following the Fontan operation; however, the timing of surgery was not associated with survival because 5 of the 11 deaths occurred in patients who had their original Fontan operation performed after 1985 (8,9). In addition, survivors were younger at the time of diagnosis, which may be reflective of earlier diagnosis and screening. There is still an increased mortality rate for patients diagnosed with PLE following the Fontan operation, but survival has markedly improved regardless of when surgery was performed.

Patients with PLE at highest risk of mortality can be identified on the basis of their hemodynamic parameters and laboratory assessment at initial diagnosis. Low cardiac index has been thought to be one of the causal factors in the development of PLE following the Fontan operation (10). Similar to previous studies, all patients in our cohort had decreased cardiac output, but those who died had a markedly decreased cardiac index compared with survivors (1.6 ± 0.4 l/min/m^2 vs. 2.7 ± 0.7 l/min/m^2, respectively). Further evidence of low cardiac output as a risk factor for mortality included lower mixed venous saturation, NYHA functional class >II, and higher serum creatinine levels in patients who died in this cohort (**Table 2**, **Fig. 2**).

The causes of low cardiac output were multifactorial. Patients who had mean pressures >15 mm Hg within the Fontan pathway had decreased survival. In addition, those patients with PLE who died had higher pulmonary vascular resistance compared with survivors. Both high Fontan pressures and high pulmonary vascular resistance impede passive venous return to the Fontan pathway, resulting in decreased cardiac output. Decreased ventricular function also was associated with decreased survival and represents another etiology for decreased cardiac output. Interestingly, there was no statistical significance for the relationship between ventricular morphology and survival. Atrial arrhythmias were common, occurring in 67% of our patient cohort. Although the presence of atrial arrhythmias was associated with decreased survival, these results were not statistically significant. Patients who were responsive to antiarrhythmic therapy had improved symptom control, likely due to improved cardiac output.

All patients with PLE should undergo a comprehensive evaluation, as described in **Table 4**. Evaluation is focused on determining both cardiac and noncardiac causes of low cardiac output. Consultation with a gastroenterologist is recommended to rule out other causes of PLE. In addition, evaluation should be performed to rule out other causes of protein loss, such as nephrotic syndrome. Hepatic dysfunction has been increasingly recognized in patients following the Fontan operation (11). Assessment of hepatic dysfunction is important because certain therapies, such as budesonide, are metabolized through the liver (12). In addition, bleeding risk may be increased in patients with hepatic dysfunction and should be considered before the initiation of heparin therapy (13).

Because the cause of PLE can be multifactorial, it is important to individualize the treatment plan for each patient (14). A thorough, systematic approach is needed to address all possible etiologies. A suggested algorithm for treatment of PLE following the Fontan



CENTRAL ILLUSTRATION **Treatment Algorithm for PLE After the Fontan Operation**

Therapies must be individualized for each patient given the number of possible contributing factors. ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CR = controlled release; IV = intravenous; PDE5 = phosphodiesterase 5; other abbreviations as in Figures 1 and 2.

operation is presented in the Central Illustration. Most patients in our cohort required multiple treatment strategies, and an aggressive approach was used to treat any potential causative factor.

For symptomatic patients, hospital admission should be considered for stabilization, beginning with a systematic evaluation and followed by initiation of medical therapy with diuretics and albumin infusion. Although albumin levels at diagnosis were not associated with survival, administration of diuretics with albumin helps correct volume overload and stabilize patients by transiently improving intravascular volume. The first step in treatment should be aimed at addressing any cardiac etiologies, specifically relieving any mechanical obstructions and improving cardiac output (15). Atrial tachyarrhythmias should be treated with cardioversion, ablation therapy, and/or antiarrhythmic medications. Any patient with atrial arrhythmias should be adequately treated with anticoagulants. Establishing atrioventricular synchrony should be the goal of the cardiac rhythm management strategy.

Intestinal therapy is aimed at reducing enteric protein loss and improving nutritional status. Malnutrition is common in PLE due to the fecal protein and fat loss. Dietary recommendations for patients with PLE include a high-protein (≥2 g/kg/day), low-fat diet (≤25% of calories from fat) with medium-chain triglyceride supplementation. Medium-chain triglyceride supplements are absorbed directly into the bloodstream, bypassing the damaged lymphatic system in patients with PLE. Several strategies exist to decrease enteric protein loss. Subcutaneous unfractionated heparin acts as a mechanical barrier by decreasing permeability of the basal membrane to large molecules such as albumin. In addition, it

TABLE 4 Suggested Evaluation of Patients With PLE

Detailed history and physical
Onset of symptoms
Arrhythmia symptoms
Sleep apnea symptoms
GI bleeding history
Presence of ascites, edema, cyanosis
Thyroid dysfunction
Liver dysfunction
Cardiac catheterization ± cardiac MRI
Obstruction in Fontan pathway
Pressure in Fontan circuit
Pulmonary vascular resistance
Cardiac index
Mixed venous saturation
Ventricular end-diastolic pressures
Gastroenterology consultation
Evaluation for hepatic dysfunction
Rule out other etiologies of PLE
Echocardiogram
Presence of fenestration
Valve regurgitation
Ventricular function
Suggestion of Fontan obstruction
Aortic coarctation
Electrophysiology assessment (ECG, 24-h Holter monitoring, exercise testing)
Sinus node dysfunction
Atrial arrhythmias
Laboratory assessment
Complete blood count
Basic metabolic profile with BUN/Cr
Serum albumin and total protein levels
Hepatic function testing
Thyroid function testing
Serum pregnancy testing
Urine analysis for protein
Stool alpha 1 antitrypsin level

BUN = blood urea nitrogen; Cr = creatinine; ECG = electrocardiogram; GI = gastrointestinal; MRI = magnetic resonance imaging; other abbreviation as in Table 1.

may decrease inflammation and potential microthrombi to the mesenteric arteries. Budesonide, an enteric-specific steroid, also targets inflammation and has been used successfully to treat PLE in patients with preserved liver function. Extracardiac conditions that may have altered cardiac hemodynamics included anemia, thyroid dysfunction, and sleep apnea. Both intestinal- and extracardiac-directed therapy can be instituted simultaneously but should not occur in place of a thorough cardiac evaluation and treatment plan.

Surgical or interventional treatments, which were more frequently used in survivors, included relief of Fontan obstruction and creation of a fenestration within the Fontan pathway. Both therapies improve cardiac output and target elevated Fontan pressures. With fenestration creation, it is important that patients are placed on some form of anticoagulation because they are at higher risk for embolic phenomena (16). Fontan conversion from an atriopulmonary connection to an extracardiac conduit was performed in the setting of refractory atrial arrhythmias in 7 patients and to relieve Fontan obstruction in 2 patients. Fontan conversion also was used more frequently in survivors; however, Fontan revision for primary treatment of PLE has not been met with good results (17). Severe cardiac valve regurgitation was treated surgically in 4 patients, with improvement in symptoms in 3 patients. Consideration for valve repair should be made on a case-by-case basis (18). Surgical interventions carry a high risk of mortality in patients with PLE; therefore, any treatment strategy should be on the basis of the clinical case and risk to the patient (1). Cardiac transplantation has been reported as a potential treatment strategy and was successfully used in 1 of the patients within our cohort (7).

Medical treatments that were used more frequently in survivors in our cohort included sildenafil, spironolactone, and octreotide. Sildenafil, a pulmonary vasodilator, works to decrease pulmonary vascular resistance and has been shown to improve some parameters of ventricular function and exercise capacity in patients after the Fontan operation (19,20). More recently, inhaled prostacyclins have been shown to improve exercise capacity in patients following the Fontan operation and may be useful in the treatment of PLE (21). Inhaled agents have the advantage of minimal systemic side effects, such as the systemic vasodilation that has been observed with sildenafil. Spironolactone has been shown to be effective in the treatment of PLE in Fontan patients (22). Although the effects have been attributed to improved cardiac function and its diuretic properties, spironolactone also has been shown to improve endothelial cell function and reduce inflammation (23). Initial reports have been published suggesting that spironolactone, in combination with endothelin A receptor antagonists, improves exercise capacity in patients with pulmonary arterial hypertension (24). Further study is needed to determine the exact mechanism of spironolactone in patients with PLE after the Fontan operation. Octreotide, a somastatin analogue, also was used with some success in our cohort, although the experience is limited (25). Octreotide decreases lymphatic flow but does increase gallstone formation. It should not be used as an initial therapy, but as an adjunct in a treatment regimen that targets cardiac and other intestinal etiologies.

STUDY LIMITATIONS. Although this report includes a large cohort of patients with PLE following the Fontan operation, there are several limitations. All patients were evaluated at the Mayo Clinic during their disease course with PLE; however, not all patients were initially diagnosed with PLE at our center, and diagnostic studies at initial diagnosis were not available for all patients. In addition, the initial Fontan operation was performed at the Mayo Clinic in only 60% of patients. Therefore, no conclusions can be made on the incidence of PLE following the Fontan operation. Although the improved survival rate may be reflective of earlier diagnosis, referral, and treatment strategies at the Mayo Clinic, the mortality rate may actually be an underestimation because it reflects those who were well enough to pursue care at the Mayo Clinic. The survival rate reflects the population of patients with PLE following the Fontan operation seen at the Mayo Clinic from 1992 to 2010. Ventricular function at diagnosis was obtained through estimated EF from echocardiography. Assessment of ventricular function through magnetic resonance imaging was not available for most patients. Time points of follow-up were variable among patients. Therefore, detailed statistical analysis of treatment strategies was not performed.

CONCLUSIONS

PLE following the Fontan operation remains difficult to treat; however, survival has improved with improved treatment strategies. A systematic approach to evaluation and an individualized treatment plan is important to maximize effective therapy. Further multicenter studies are needed to determine the ideal treatment strategy.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: PLE occurs in 5% to 15% of patients following the Fontan operation.

COMPETENCY IN PATIENT CARE: PLE following the Fontan operation remains difficult to treat. However, survival has improved with a systematic approach to evaluation, as well as individualized treatment.

TRANSLATIONAL OUTLOOK: The etiology of PLE following the Fontan operation is multifactorial, and further studies are needed to determine the ideal treatment strategy.

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