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Fontan-associated protein-losing enteropathy and plastic bronchitis: characterizing current-era risk factors, course, and progression

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Abstract

Objective—Characterize the medical history, disease progression, and treatment of current-era patients with the rare diseases Fontan-associated protein losing enteropathy (PLE) and plastic bronchitis (PB).

Study Design—A novel survey that queried demographics, medical details, and treatment information was piloted and placed online via a Facebook portal allowing social media to power the study. Participation regardless of PLE or PB diagnosis was allowed. Case control analyses compared patients with PLE and PB to uncomplicated control Fontan patients.

Results—The survey was completed by 671 subjects including 76 with PLE, 46 with PB, and 7 with both. Median PLE diagnosis was 2.5 years post-Fontan. Hospitalization for PLE occurred in 71% with 41% hospitalized ≥ 3 times. Therapy varied significantly. PLE patients more commonly had hypoplastic left ventricle (62% vs 44% control; OR 2.8, 95% CI 1.4–5.5), chylothorax (66% vs 41%; OR 3.0, CI 1.6–5.3), and cardiothoracic surgery in addition to staged palliation (17% vs 5%; OR 4.3, CI 1.6, 11.2). Median PB diagnosis was 2 years post-Fontan. Hospitalization for PB occurred in 91% with 61% hospitalized ≥3 times. Therapy was very diverse. PB patients more commonly had chylothorax at any surgery (72% vs 51%; OR 2.5, CI 1.2–5.1) and seasonal allergies (52% vs 36%; OR 2.0, CI 1.0–3.9).

Conclusions—Patient-specific factors are associated with diagnoses of PLE or PB. Treatment strategies are diverse without clear patterns. These results provide a foundation upon which to

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design future therapeutic studies and identify a clear need for forming consensus approaches to treatment.

Introduction

In the current era, improved survival for patients with single ventricle-types of congenital heart defects, including hypoplastic left heart syndrome, has redirected the attention of research to long term patient outcomes. Important complications of the condition and its surgical management, culminating in palliation to the Fontan physiology, have become increasingly problematic as more patients survive surgery with significantly increased life expectancy. Two important complications, protein-losing enteropathy (PLE), characterized by the abnormal loss of serum protein into the enteral lumen, and plastic bronchitis (PB), characterized by formation of exudative airway casts [1], greatly impact the length and quality of life after the Fontan. Both of these conditions confer marked morbidity and high mortality following diagnosis [2–5], but care of the patients with these complications is hampered by limitations in the current understanding of these diseases. The last multicenter study of PLE was published more than 15 years ago [3], predating the modern surgical era and advances in surgical management, perioperative care and medical therapy. Recent studies of PLE consist of single center case series and case-control studies. Medical literature for PB is even more limited and is made up almost entirely of case reports and case series. Further, no cross-sectional reports describing the scope of either PLE or PB are published; this leads to a lack of knowledge regarding risk factors for disease development, the current spectrum of disease severity, and current treatment practices.

The lack of data for PLE and PB is largely attributable to disease rarity; both diseases occur in a relatively small percentage of Fontan patients [2, 6, 7]. Single centers do not have a sufficient number of patients to adequately power studies. Multicenter research, though necessary to effectively study rare diseases using traditional methods, has been limited[8] and still involves a relatively small number of patients. Conversely, larger patient groups are known to gather “virtually” online in various social media forums. We hypothesized that by offering participation in research online, patients with PLE or PB would participate in larger numbers than would be obtainable even through multicenter collaboration. Accordingly, for this study we used a novel, online survey to collect patient-reported information regarding PLE and PB risk factors, clinical course, and treatment.

Methods

Study Design

The methodology for this study has been previously published[9]. In brief, this survey assessed in detail Fontan complication-specific symptoms, diagnoses, and treatments by obtaining patient-reported information from post-Fontan palliation individuals with and without PLE or PB. The survey was designed with the specific intent of conducting case-control analyses between patients with and without one or both of these complications. The survey was posted online and utilized patient-run social media communities to access respondents. The study was approved by the University of Michigan’s Institutional Review Board, and an informed consent message preceded the survey.

Survey instrument

A survey tool was designed consisting of questions regarding patient demographics, medical and surgical history, symptoms, associated illnesses, home environment, treatment history, and current medical therapy with specific questions regarding symptoms and treatments related to PLE and PB. The survey was structured to encourage the participation of patients or parents of patients who had a Fontan procedure, regardless of whether or not they had been diagnosed with PLE or PB. The instrument was piloted in talk-aloud sessions with patients who had a Fontan procedure and their parents, and included patients with and without complications such as PLE and PB. The instrument was refined based on feedback received. The final survey consisted of 31 questions/items for uncomplicated Fontan patients, 52 items for patients with PLE, 55 items for patients with PB, and 76 items for patients with both. A copy of the survey is available for viewing at this website: http://tinyurl.com/UmichFontanSurvey. The survey was linked to two online portals from which patients could gain access: a study specific Facebook page (https://www.facebook.com/#!/UMFontan) and a web-based portal from the University of Michigan Congenital Heart Center's home page. The survey was administered using Qualtrics survey software (Provo, Utah), which includes dynamic routing capabilities. The survey was anonymous and took care to avoid collecting any personal identifying information. Participants were offered a summary of the findings at study conclusion as compensation; no other compensation for participation was given.

Response validation

A series of planned quality control measures were used to assess response validity. Surveys that did not include birth years and years of operations were excluded. Responses in which birthdate, surgical dates, and Fontan complication onset did not follow a feasible chronologic pattern were also excluded.

As an additional analysis to support external validity of the survey for the total Fontan population, we compared our participants' demographic and historical information to patients reported in a recent Fontan cross-sectional study [10] performed by the Pediatric Heart Network (PHN).

Statistical Analysis

Standard descriptive statistics outlined participant characteristics overall and were stratified by "uncomplicated", "PLE", "PB", and "both PLE and PB". We matched "uncomplicated" Fontan patients 2:1 or 3:1 with complicated Fontan patients (i.e. those with a diagnosis of PLE or PB, respectively) by year of Fontan surgery. Post-match examination of time from Fontan to study participation assured the control groups were not made up of a large percentage of patients < 1 year from Fontan surgery who would be at higher risk of still developing PLE or PB thereby making them not true controls. Group comparisons between PLE or PB and their matched controls were then made in each participant characteristic using Chi-square tests or Fisher's exact tests, as appropriate, for categorical variables and Wilcoxon rank sum tests for continuous variables. Odds ratios and 95% confidence intervals for being diagnosed with PLE or PB were also reported. For the validation with the existing Fontan cross-sectional study, we used two-group comparisons including Chi-square test and

t-test. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA). P-value < 0.05 was considered statistically significant.

Results

A total of 855 individuals with a Fontan palliation completed at least one survey question. Of these, a total of 671 respondents (78%) including 76 with PLE, 46 with PB, and 7 with both PLE and PB completed the survey and were included in the analysis. Demographics, medical, and surgical history for the cohort overall, stratified by complication, are shown in Table 1. Additionally, 1.6% of patients reported having undergone heart transplantation following Fontan: 3 had PLE, 3 had PB, 1 had both PLE/PB, and 4 were non-PLE or PB Fontan patients.

PLE symptoms and treatment

A majority of participants reporting PLE were male (59%), with a median age of 11 years (IQR 7–17.5) at the time of survey. Median time following Fontan to diagnosis of PLE was 2.5 years (IQR 1–6). The large majority of PLE patients reported having symptoms chronically, with swelling in the abdomen (82%) and extremities (46%) being the most commonly reported. A relatively low number of patients reported having chronic diarrhea (20%). A majority (84%) of patients reported that symptoms were present during all 4 seasons, and there was no specific seasonal difference in severity for the cohort overall. Increased severity of symptoms were associated with viral infections for 66% of respondents and associated with allergies for 9% of respondents. In total, 71% of respondents reporting a PLE diagnosis had been hospitalized for treatment of the condition at least once since diagnosis; 30% of the respondents had been admitted 1–2 times, 20% were admitted 3–5 times, 11% were hospitalized 6–10 times, 5% were hospitalized 11–20 times, and 5% reported >20 hospitalizations.

Treatments varied widely among PLE patients. Daily treatments reported by respondents included a high protein diet (53%), enteral budesonide (36%), sildenafil (32%), prednisone (12%), IV or subcutaneous heparin (5%), and octreotide (4%); 24% reported no daily therapy. Only 26% of patients reported being on more than one daily treatment; high protein diet and budesonide was the most prevalent combination. Daily treatment with budesonide was significantly associated with both increased hospital admissions (p=0.003) and increased emergency department visits (p=0.048). No other associations between hospitalization and treatments were noted. An additional 24% of patients reported chronically receiving IV albumin on an outpatient basis with a widely varying interval between infusions. Participants reported PLE flares were treated most often with IV albumin (in 42% of patients), followed by blood transfusions (13%), and IV steroids (4%). The providers treating PLE patients were reported as cardiologists (93%), gastroenterologists (25%), primary care pediatrician or internist (15%), family practice provider (5%), immunologist (2%), and endocrinologist (1%) (subjects could report more than 1 provider).

PLE case-control analysis

Results of the case-control analysis with uncomplicated Fontan patients are shown in Table 2. Only 2/152 control patients were <1 year from Fontan at the time of participation. Participants with PLE had significantly increased odds of having a morphologic right ventricle as their single ventricle. Those with PLE had higher odds of having had an additional intra-cardiac or great vessel surgery beyond the typical 3-stage single ventricle palliation and were more likely to have had a diaphragm plication. For PLE participants, there was an increased odds of chylothorax at any point in their past medical history and an increased odds of requiring treatment for a chylothorax, including special formula or diet, thoracic duct ligation, and/or pleurodesis.

Medications taken by both PLE and control patients are shown in Table 3. Notably with regard to non-PLE-specific medications, PLE patients were significantly more likely to take a daily antibiotic, diuretics, digoxin, sildenafil, spironolactone, an inhaled steroid or bronchodilator, and warfarin. They were less likely to take aspirin.

Respondents also reported growth information (Table 2). PLE patients and control Fontan patients were similar in weight, but PLE patients reported significantly lower heights compared to control Fontans. To further evaluate growth parameters, body mass index (BMI) was calculated for each patient. The PLE group had both more underweight (< 5th %ile on the CDC growth chart) and with markedly elevated BMI (> 95th%ile on the CDC growth chart) individuals than the control Fontan patients. On further analysis, the PLE patients with BMI >95%ile were more likely take budesonide than PLE patients with normal BMI (31.6% vs. 8.1%; p=0.01).

PB symptoms and treatment

A majority of participants reporting PB (N=46) were male (59%), and the median respondent age at survey was 7.5 years-old (IQR 6–12). The median time to diagnosis of PB was 2 years after Fontan (IQR 1–6 years). Those with PB described symptoms during all seasons, but unlike the PLE group, a majority of PB reported symptoms were most severe in the winter. A large majority (80%) of PB patients reported that symptoms were associated with developing cold or upper respiratory infection. Only 9% of respondents diagnosed with PB reported never being hospitalized as a result of PB. Among the other PB patients, 28% had been hospitalized 1–2 times, 30% had been hospitalized 3–5 times, 15% had been hospitalized 6–10 times, 9% were hospitalized 11–20 times, and 7% had been hospitalized >20 times.

Treatment for PB varied widely. Daily PB-specific treatments included inhaled albuterol (41%), chest physiotherapy (26%), inhaled budesonide (26%), inhaled dornase-alpha (24%), inhaled tissue plasminogen activator (tPA) (22%), hypertonic saline (20%), and oral steroids (20%). For acute PB flares, patients reported increased usage of oral/systemic steroids (39%) and inhaled tPA (46%). Additionally, 52% of patients reported requiring at least one therapeutic bronchoscopy to remove a cast. In contrast to the PLE cohort, a majority (67%) of the PB cohort reported being on more than one daily treatments to control their PB

symptoms. However, no medication or medication combination was associated with a lower incidence of hospitalization or emergency department visits.

PB case-control analysis

The case-control analysis comparing PB patients to control Fontan patients demonstrated that PB patients were more likely to have had a diaphragm plication, more likely to have had a chylothorax following a cardiac operation, and were more likely to report allergies (Table 4.) No control patient was less than 1 year post-Fontan at the time of participation. In comparison to PLE, there were non-significant trends associating PB with single right ventricle (p=0.12) or with additional major cardiac surgery (p=0.09).

The complete summary of medications for PB and control patients is shown in Table 3. With regards to non-PB-specific medications, PB patients take significantly more daily antibiotics, bosentan, diuretics, digoxin, sildenafil, spironolactone, and warfarin when compared to control Fontan patients. PB patients are less likely to take aspirin.

Growth parameters including height, weight, or BMI in PB patients were not different compared to control Fontan patients.

Patients with both PLE and PB

Seven respondents reported having both PLE and PB with a median age of 11 years (IQR 7–13 years) at the time of survey. A single right ventricle was present for 71% (n=5) of this subset. For this group, PLE diagnosis preceded PB diagnosis or the diagnoses occurred simultaneously in the majority of cases. The diagnosis of at least one of the conditions occurred early after the Fontan; median time from Fontan to diagnosis was 1 year (IQR 0–2 years) for PLE and 1 year (IQR 0–7 years) for PB. The small number of patients precluded further analyses.

Comparison to other Fontan reports

To evaluate whether the online respondents appeared similar to the overall Fontan population, our cohort was compared to the recent PHN Fontan cross-sectional study [10]. There were no differences between the two populations in terms of gender (60% vs. 63% male; p=0.34), mean age at Fontan (3.4 years vs. 3.3 years; p=0.42), or type of heart disease (49% vs. 43% hypoplastic left ventricle, 34% vs. 36% hypoplastic right ventricle, 18% vs. 17% non-specific single ventricle; p=0.62) between the PHN study and our study, respectively.

Discussion

Through this study of a large, contemporary, cross sectional, international cohort of Fontan patients, we have been able to describe the current spectrum of PLE and PB, including the presentation, the clinical course, and the range of therapeutic approaches. As such, it represents an essential “starting point” for the development of multicenter collaborative efforts to further define risk factors and evaluate the efficacy of specific treatment protocols.

Prior to this study, most information related to PLE and PB was gleaned from single center experiences. Mertens and colleagues performed a multicenter European study of 114 patients with Fontan physiology diagnosed with PLE from 1975–1995 [2]. Compared to Mertens, our study found a higher percentage of hypoplastic left ventricle patients (with and without unspecified ventricle type, 62–80% in our study vs. 7–32% in Mertens) and an earlier age at the time of Fontan operation (median age 3 years vs. 8.2 years). The Mertens study is valuable as it remains the only large, multicenter PLE patient cohort reported. However, due to the earlier era for single ventricle therapy, this cohort likely differs from current PLE patients in terms of heart disease, course, and treatment. Several smaller single-center reports have presented their own experience with PLE, but to maximize numbers, patients who were evaluated and treated in the past were included [6]. Similarly, no detailed study of large numbers of current PB patients has been reported, and the literature is made up nearly entirely of limited, single center descriptions that rely, at least in part, on historical information [4, 11, 12].

To recruit the numbers of patients required to identify specific risk factors associated with the development of PLE and PB in the current era, we used the power of social media to access the online Fontan community, and in doing so, we examined the largest cohort of patients with PLE reported in the last 15 years and the largest cohort of patients with PB ever reported. Despite the wide range in disease phenotypes and therapeutic approaches, some important patterns emerge which will allow the development of hypotheses for future prospective studies. By structuring the study to allow for case-control analyses, risk factors for the diagnosis of PLE or PB were found and can therefore be used to advance understanding of disease pathogenesis and to develop novel therapeutic strategies.

The first step in assessing our results was to develop a profile of the Fontan patient who develops either PLE or PB. For PLE patients, the condition is diagnosed approximately 2.5 years after Fontan, is typified by abdominal fullness and peripheral edema, and results in a modest number of hospitalizations over the course of the illness. A typical PB patient is diagnosed 2 years after Fontan and has increased symptoms in the winter; the exacerbations are commonly associated with a viral infection, and lead to multiple hospitalizations.

The next step in analysis was to identify specific factors which are associated with the development of PLE and PB in an effort to provide insight into disease pathogenesis, an incomplete understanding of which has slowed the development of new and more effective therapies. Several studies have postulated potential causes of these conditions [13–16]. However, substantiated comprehensive, mechanistic descriptions are still lacking and case-control studies will be required to identify predisposing or associated factors. The two case-control studies of risk factors for PLE [18, 19] largely involve patients from a slightly earlier era, and their findings may or may not translate to the current Fontan population. Only one case-control study of PB patients has been performed [17], and it included patients diagnosed with PB over a long historical period.

The present study, specifically designed to allow a control Fontan group to participate, was able to demonstrate that some of the proposed risk factors for PLE and PB, which were based on small or earlier era cohorts, are associated with an increased odds of being

diagnosed with PLE or PB in the current era. PLE was associated with (i) systemic right ventricle, (ii) chylous and prolonged chest tube drainage after surgery and (iii) major cardiac surgeries in addition to the typical 3-stage palliation. Each of these associations has been previously demonstrated in small, retrospective single center studies [13, 18, 19], but never confirmed in a multicenter analysis. For PB, single right ventricle and lymphatic abnormalities have been suggested in case reports, but never confirmed in a large, controlled study [4, 14, 20].

The study also revealed some important features of PLE and PB that have not been previously reported or are not widely appreciated. First, with regard to PLE symptomatology, only 20% of PLE patients reported having chronic diarrhea, a symptom that has been used to identify patients at risk for PLE. The relative rarity of chronic diarrhea in patients with PLE may signify that the presence of diarrhea is not a reliable screening tool to identify patients at risk for developing PLE and that routine surveillance for low serum protein levels may be necessary. Abdominal swelling, present in 82% of patients with PLE, may be the best symptom to screen for to trigger further evaluation. The finding that PLE patients were more likely to have had prolonged and chylous chest tube drainage than those without was not surprising but was important to demonstrate. Perhaps more surprising was the finding of “weight dysregulation” in patients with PLE. PLE patients were more likely to be over- or underweight. Failure to gain weight is perhaps not unexpected in some patients due to nutritional compromise by the PLE process. The increased risk of elevated BMI is more difficult to explain and may be related to endocrine abnormalities that are anecdotally reported but are not well understood [16, 21]. Further, BMI >95ile was associated with oral budesonide treatment. There are two potential (and not necessarily mutually exclusive) explanations. First, PLE patients may have elevated BMI due to fluid retention and not adiposity; it may be that individuals on budesonide therapy were more likely to retain fluid. Alternatively, this may represent an actual obese group of PLE patients. In this case, whether budesonide could be causative remains unknown, but the association raises concern about significant systemic steroid effects from this treatment. With regard to PB symptomatology, the association between PB and allergies is novel. Interestingly, a recent study of PB cast proteomics suggested that Fontan PB casts are inflammatory in nature [1]; the association between allergies and PB provides further evidence there is an immune or inflammatory component of PB, and it could be a new target for future therapy.

Although there is no current “standard of care” for PLE or PB, the spectrum of current treatment practices was assessed. In addition, we evaluated the extent to which potentially efficacious therapies for PLE and PB (as described in individual cases or small case series [22–26]) were being used in practice. As might be expected, this study demonstrated wide variation in treatment practices. Interestingly, only 26% of individuals were being treated with more than one PLE-specific therapy despite 41% of individuals being hospitalized ≥3 times specifically as a result of PLE. This lack of escalation in therapy despite increasing disease severity is striking and likely reflects the paucity of a clear “best practice” guidelines for PLE management. In contrast, the majority of PB patients reported taking multiple daily medications. The most commonly prescribed medicines in patients with PLE and PB, including diuretics and ACE inhibitors, are not disease-specific. Of the PLE disease-specific therapies, oral budesonide was the most widely prescribed and tended

to be used in patients with more advanced disease as evidenced by increased hospital admission and emergency department visits. The alternative explanation, oral budesonide use leads to a more severe clinical course, seems unlikely given the number of studies demonstrating its efficacy in improving PLE symptomatology [25, 26]. The tendency to use more disease-specific therapy in those patients with more advanced disease obscures the ability to identify therapeutic approaches which improve outcomes using this approach and reinforces the need for prospective, placebo-controlled trials. Given the current variability in treatment approaches, the first step may be to establish a consensus best practice and identify therapies suitable for randomized trials.

This study has limitations that were discussed in the methodology paper previously published[9]. However, a summary of the limitations is warranted. First, the participants may not be representative of the total population of Fontan patients. However, for gender, age, and heart-disease etiology, our cohort was not different from the PHN Fontan cohort [10] which suggests similarity between our participants and the overall Fontan population. Second, many pieces of specific information, such as hemodynamic measurements at cardiac catheterization, that would be of significant interest that were not obtainable using this patient-reporting approach. Third, because the study was anonymous, there was no way to validate the participants' responses using traditional methods in clinical research, such as comparison to the medical record. It is possible that concerned parents may self-diagnose and report PLE or PB in their children in this survey format, and given the same patient, pediatric cardiologists may not have made the same diagnoses. Fourth, with regard to risk factor analysis, we are only able to report bivariate odds ratios. Given the limitations in patient reported data, a multivariable analysis to identify independent risk factors or predict overall risk of disease stemming from this study would lack some potential risk factors of interest, and the results of such an analysis might be misleading. Finally, we cannot assure that individuals who claimed to be Fontan patients actually were Fontan patients or had the complications that they reported. However, with no incentive other than advancing knowledge of their own disease process, individuals should have had no motivation to knowingly provide false information. The study design allowed the information queried to be provided by patients, and survey piloting demonstrated this to be true. The study's validity checks assured that reported information made medical sense. All of these points indicate the study's results are likely to be accurate. For rare diseases with significant knowledge limitations, this approach to data collection fills knowledge gaps and permits the development of well-founded hypotheses for testing in prospective trials.

Conclusion

Through a novel approach to studying rare diseases, this study was able to gather patient-reported data regarding the typical appearance and treatment of Fontan-associated PLE and PB. Additionally, using a case-control approach, specific risk factors associated with disease diagnosis were identified. This study gives insight into the clinical disease spectrum and risk factors for PLE and PB in the current era and provides a framework on which to build best practice guidelines and to develop prospective clinical trials.

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Abbreviations

PLE	Protein-losing enteropathy
PB	Plastic Bronchitis

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Table 1

Demographic and Clinical Characteristics of Respondents

	Overall (n=671)	PLE (n=76)	PB (n=46)	Both (n=7)
Respondent				
Parent	637 (94.9)	69 (90.8)	46 (100)	7 (100)
Patient	34 (5.1)	7 (9.2)	0 (0.0)	0 (0.0)
Male sex	421 (62.7)	45 (59.2)	27 (58.7)	4 (57.1)
Age at survey (yrs), Median (IQR)	7 (5–12)	11 (7–17.5)	7.5 (6–12)	11 (7–13)
Clinical				
Heart disease etiology				
Hypoplastic left ventricle	311 (46.3)	47 (61.8)	25 (54.3)	5 (71.4)
Hypoplastic right ventricle	244 (36.4)	15 (19.7)	11 (23.9)	1 (14.3)
Non-specific single ventricle	116 (17.3)	14 (18.4)	10 (21.7)	1 (14.3)
Age at Fontan (yrs), Median (IQR)	3 (2–4)	3 (2–4)	3 (2–4)	3 (2–3)
Time since Fontan (yrs), Median (range)	4 (2–9)	8 (4–13)	4.5 (3–9)	8 (4–10)
Other surgeries*				
Norwood	319 (47.5)	45 (59.2)	26 (56.5)	4 (57.1)
BT shunt	291 (43.4)	23 (30.3)	21 (45.7)	1 (14.3)
PA banding	81 (12.1)	11 (14.5)	3 (6.5)	0 (0.0)
Hemifontan	114 (17.0)	20 (26.3)	12 (26.1)	2 (28.6)
Glenn	515 (76.87)	50 (65.8)	33 (71.7)	5 (71.4)
Diaphragm plication	30 (4.5)	9 (11.8)	6 (13.0)	2 (28.6)
Other major intracardiac/great vessel procedure	43 (6.4)	13 (17.1)	6 (13.0)	2 (28.6)
History of a chylous pleural effusion	316 (47.1)	50 (65.8)	33 (71.7)	6 (85.7)
History of a thoracic duct ligation	25 (3.7)	10 (13.2)	3 (6.5)	0 (0.0)
History of a pleurodesis	25 (3.7)	10 (13.2)	5 (10.9)	2 (28.6)

All values represent N (%) unless otherwise specified; column percentages reported.

BT = Blalock-Taussig, PA = pulmonary artery

*Categories are not mutually exclusive

Table 2

Comparison of the demographic and clinical characteristics of survey participants with or without protein losing enteropathy (PLE) following Fontan palliation (N=228)

	PLE				
Characteristics	**Yes (N=76)**	**No (N=152)**	**p-value[§]**	**OR**	**95% CI**
Male sex	45 (59.2)	94 (61.8)	0.65	0.88	0.50, 1.55
Age at survey, years	11 (7–17.5)	10.5 (7–16.5)	0.72	1.00	0.96, 1.03
Age at Fontan, years	3 (2–4)	3 (2–4)	0.68	0.94	0.83, 1.06
Caucasian	66 (86.8)	122 (80.3)	0.05	2.32	0.97, 5.57
Heart disease etiology					
Hypoplastic left ventricle	47 (61.8)	67 (44.1)		2.81	1.43, 5.53
Hypoplastic right ventricle	15 (19.7)	60 (39.5)	0.01	Ref	
Non-specified single ventricle	14 (18.4)	25 (16.4)		2.24	0.94, 5.32
Other surgery					
Norwood	45 (59.2)	69 (45.4)	0.049	1.75	1.00, 3.05
BT shunt	23 (30.3)	66 (43.4)	0.05	0.57	0.32, 1.02
PA band	11 (14.5)	16 (10.5)	0.38	1.44	0.63, 3.28
Hemifontan (Stage II)	20 (26.3)	35 (23.0)	0.58	1.19	0.63, 2.25
Bidirectional Glen (Stage II)	50 (65.8)	102 (67.1)	0.84	0.94	0.53, 1.69
Diaphragm plication	9 (11.8)	4 (2.6)	0.01	4.93	1.49, 19.0
Other major cardiac procedures	13 (17.1)	7 (4.6)	0.002	4.27	1.63, 11.2
Chylothorax	50 (65.8)	62 (40.8)	0.0002	2.96	1.65, 5.31
Drained with a chest tube	46 (92.0)	57 (91.9)	1.00	1.01	0.24, 4.44

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Characteristics	PLE		p-value[§]	OR	95% CI
	Yes (N=76)	No (N=152)			
Treated with a special formula	22 (44.0)	13 (21.0)	0.01	2.91	1.25, 6.77
Treated with thoracic duct ligation	10 (20.0)	3 (4.8)	0.01	5.04	1.31, 19.5
Treated with pleurodesis	10 (20.0)	4 (6.5)	0.03	3.65	1.07, 12.5
Allergies	27 (35.5)	57 (37.5)	0.85	0.95	0.53, 1.69
Celiac disease	3 (3.9)	1 (0.7)	0.11	6.20	0.65, 166
Intestinal malrotation	3 (3.9)	5 (3.3)	1.00	1.22	0.23, 5.41
Weight at survey, kg	29.3 (19.1–43.2)	29.8 (19.5–52.3)	0.25	0.99	0.97, 1.004
Height at survey, cm	126 (107–150)	135 (112–163)	0.03	0.99	0.98, 0.999
Body mass index at survey, kg/m^2	18.0 (15.9–22.0)	17.6 (15.4–20.8)	0.38	1.04	0.98, 1.11
Underweight	13 (17.1)	14 (9.2)	0.003	2.67	1.14, 6.28
Normal	32 (42.1)	92 (60.5)		Ref	
Overweight	6 (7.9)	17 (11.2)		1.02	0.37, 2.80
Obese	12 (15.8)	7 (4.6)		4.93	1.79, 13.6
unknown	13 (17.1)	22 (14.5)			

[*] Data are presented as N (%) for categorical variables and Median (25th percentile – 75th precentile) for continuous variable.

BT = Blalock-Taussig, PA = pulmonary artery

[§] P-value from Chi-square tests or Fisher's exact tests, as appropriate, for categorical variables and Wilcoxon rank sum tests for continuous variables on comparison of each characteristic between the patients with/without PLE.

Table 3

Description of the general medication use of survey participants following Fontan palliation

	Healthy Fontans[¥] (N=290)	PLE			PB		
General medications taking daily	**N (%)**	**Yes (N=76)**	**No (N=152)**	**p-value[§]**	**Yes (N=46)**	**No (N=138)**	**p-value[†]**
Albuterol or Levalbuterol	11 (3.8)	11 (14.5)	5 (3.3)	0.002	15 (32.6)	6 (4.3)	<.0001
Allergy medicine	33 (11.4)	15 (19.7)	16 (10.5)	0.06	11 (23.9)	17 (12.3)	0.06
Amlodipine	1 (0.3)	1 (1.3)	0 (0.0)	0.33	0 (0.0)	1 (0.7)	1.00
Antibiotics (any daily antibiotic)	8 (2.8)	8 (10.5)	3 (2.0)	0.01	13 (28.3)	5 (3.6)	<.0001
Aspirin	230 (79.3)	44 (57.9)	118 (77.6)	0.002	27 (58.7)	112 (81)	0.002
Atenolol	12 (4.1)	2 (2.6)	8 (5.3)	0.50	0 (0.0)	4 (2.9)	0.57
Bosentan	1 (0.3)	0 (0.0)	0 (0.0)	N/A	3 (6.5)	1 (0.7)	0.049
Budesonide oral	0 (0.0)	26 (34.2)	0 (0.0)	<.0001	0 (0.0)	0 (0.0)	N/A
Bumetanide	0 (0.0)	3 (3.9)	0 (0.0)	0.04	1 (2.2)	0 (0.0)	0.25
Captopril	14 (4.8)	6 (7.9)	9 (5.9)	0.57	5 (10.9)	5 (3.6)	0.12
Carvedilol	13 (4.5)	3 (3.9)	7 (4.6)	1.00	6 (13.0)	6 (4.3)	0.08
Chlorothiazide	1 (0.3)	10 (13.2)	1 (0.7)	<.0001	4 (8.7)	0 (0.0)	0.004
Digoxin	37 (12.8)	23 (30.3)	24 (15.8)	0.01	11 (23.9)	13 (9.4)	0.01
Diltiazem	2 (0.7)	0 (0.0)	2 (1.3)	0.55	0 (0.0)	0 (0.0)	N/A
Enalapril	115 (39.7)	37 (48.7)	55 (36.2)	0.07	19 (41.3)	60 (43.5)	0.80
Furosemide	42 (14.5)	57 (75.0)	26 (17.1)	<.0001	26 (56.5)	16 (11.6)	<.0001
Heparin -Subcutaneous injection	1 (0.3)	1 (1.3)	1 (0.7)	1.00	2 (4.3)	0 (0.0)	0.06
Inhaled steroid	12 (4.1)	8 (10.5)	5 (3.3)	0.03	15 (32.6)	7 (5.1)	<.0001

General medications taking daily	Healthy Fontans[¥] (N=290) N (%)	PLE Yes (N=76)	PLE No (N=152)	PLE p-value[§]	PB Yes (N=46)	PB No (N=138)	PB p-value[†]
Inhaled tPA	0 (0.0)	1 (1.3)	0 (0.0)	0.33	10 (21.7)	0 (0.0)	<.0001
Lisinopril	35 (12.1)	13 (17.1)	17 (11.2)	0.21	4 (8.7)	18 (13.0)	0.43
Losartan	3 (1.0)	1 (1.3)	1 (0.7)	1.00	0 (0.0)	2 (1.4)	1.00
Metoprolol	2 (0.7)	3 (3.9)	2 (1.3)	0.34	0 (0.0)	0 (0.0)	N/A
Octreotide	0 (0.0)	3 (3.9)	0 (0.0)	0.04	0 (0.0)	0 (0.0)	N/A
Prednisone	0 (0.0)	4 (5.3)	0 (0.0)	0.01	6 (13.0)	0 (0.0)	0.0002
Propranolol	1 (0.3)	0 (0.0)	1 (0.7)	1.00	0 (0.0)	0 (0.0)	N/A
Sildenafil	8 (2.8)	24 (31.6)	4 (2.6)	<.0001	18 (39.1)	4 (2.9)	<.0001
Spironolactone	24 (8.3)	40 (52.6)	16 (10.5)	<.0001	13 (28.3)	8 (5.8)	<.0001
Verapamil	0 (0.0)	0 (0.0)	0 (0.0)	N/A	0 (0.0)	0 (0.0)	N/A
Warfarin	56 (19.3)	30 (39.5)	33 (21.7)	0.005	16 (34.8)	23 (16.7)	0.01
Other	73 (25.2)	36 (47.4)	41 (27.0)	0.002	24 (52.2)	32 (23.2)	0.0002
Taking medication daily but don't know the name	0 (0.0)	0 (0.0)	0 (0.0)	N/A	1 (2.2)	0 (0.0)	0.25

[*] Data are presented as N (%).

[¥] Healthy Fontans matched with either PLE or PB based on year of Fontan procedure done.

[§] P-value from Chi-square tests or Fisher's exact tests on comparison of each medication between the patients with/without PLE.

[†] P-value from Chi-square tests or Fisher's exact tests on comparison of each medication between the patients with/without PB.

Table 4

Comparison of the demographic and clinical characteristics of survey participants with or without plastic bronchitis (PB) following Fontan palliation (N=184)

	PB				
Characteristics	**Yes (N=46)**	**No (N=138)**	**p-value[§]**	**OR**	**95% CI**
Male sex	27 (58.7)	88 (63.8)	0.54	0.81	0.41, 1.60
Age at survey, years	7.5 (6–12)	8 (6–12)	0.67	0.99	0.92, 1.06
Age at Fontan, years	3 (2–4)	3 (2–4)	0.11	0.82	0.63, 1.08
Caucasian	39 (84.8)	116 (84.1)	0.85	0.91	0.36, 2.34
Heart disease etiology					
Hypoplastic left ventricle	25 (54.3)	57 (41.3)		2.23	1.00, 4.97
Hypoplastic right ventricle	11 (23.9)	56 (40.6)	0.12	Ref	
Non-specified single ventricle	10 (21.7)	25 (18.1)		2.24	0.77, 5.41
Other surgery					
Norwood	26 (56.5)	57 (41.3)	0.07	1.85	0.94, 3.63
BT shunt	21 (45.7)	68 (49.3)	0.67	0.87	0.44, 1.69
PA band	3 (6.5)	20 (14.5)	0.16	0.41	0.12, 1.46
Hemifontan (Stage II)	12 (26.1)	21 (15.2)	0.10	1.97	0.88, 4.40
Bidirectional Glen (Stage II)	33 (71.7)	112 (81.2)	0.18	0.59	0.27, 1.27
Diaphragm plication	6 (13.0)	5 (3.6)	0.03	3.95	1.10, 14.8
Other major cardiac procedures	6 (13.0)	7 (5.1)	0.09	2.79	0.84, 9.09
Chylothorax	33 (71.7)	70 (50.7)	0.01	2.47	1.20, 5.08
Drained with a chest tube	31 (93.9)	65 (92.9)	1.00	0.95	0.16, 7.79

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Characteristics	PB		p-value[§]	OR	95% CI
	Yes (N=46)	No (N=138)			
Treated with a special formula	18 (54.5)	18 (25.7)	0.005	3.54	1.44, 8.68
Treated with thoracic duct ligation	3 (9.1)	2 (2.9)	0.32	3.42	0.49, 30.0
Treated with pleurodesis	5 (15.2)	2 (2.9)	0.03	6.08	1.13, 47.6
Allergies	24 (52.2)	49 (35.5)	0.045	1.98	1.01, 3.89
Weight at survey, kg	24.1 (18.2–44.1)	25.0 (19.1–44.1)	0.58	1.00	0.98, 1.02
Height at survey, cm	122 (109–150)	122 (112–147)	0.71	1.00	0.98, 1.01
Body mass index at survey, kg/m^2	16.8 (15.4–18.6)	16.8 (15.1–19.8)	0.98	0.99	0.91, 1.08
Underweight	6 (13.0)	14 (10.1)	0.71	1.30	0.45, 3.77
Normal	24 (52.2)	73 (52.9)		Ref	
Overweight	6 (13.0)	14 (10.1)		1.30	0.45, 3.77
Obese	3 (6.5)	16 (11.6)		0.57	0.15, 2.13
unknown	7 (15.2)	21 (15.2)			

[*] Data are presented as N (%) for categorical variables and Median (25th percentile – 75th precentile) for continuous variable.

BT = Blalock-Taussig, PA = pulmonary artery

[§] P-value from Chi-square tests or Fisher's exact tests, as appropriate, for categorical variables and Wilcoxon rank sum tests for continuous variables on comparison of each characteristic between the patients with/without PB.