Fontan-Associated Protein-Losing Enteropathy and Plastic Bronchitis

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Objective To 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.

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 plastic bronchitis diagnosis was allowed. Case control analyses compared patients with PLE and plastic bronchitis with uncomplicated control patients receiving the Fontan procedure.

Results The survey was completed by 671 subjects, including 76 with PLE, 46 with plastic bronchitis, 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. Patients with PLE more commonly had hypoplastic left ventricle (62% vs 44% control; OR 2.81, 95% CI 1.43-5.53), chylothorax (66% vs 41%; OR 2.96, CI 1.65-5.31), and cardiothoracic surgery in addition to staged palliation (17% vs 5%; OR 4.27, CI 1.63-11.20). Median plastic bronchitis diagnosis was 2 years post-Fontan. Hospitalization for plastic bronchitis occurred in 91% with 61% hospitalized ≥3 times. Therapy was very diverse. Patients with plastic bronchitis more commonly had chylothorax at any surgery (72% vs 51%; OR 2.47, CI 1.20-5.08) and seasonal allergies (52% vs 36%; OR 1.98, CI 1.01-3.89).

Conclusions Patient-specific factors are associated with diagnoses of PLE or plastic bronchitis. Treatment strategies are diverse without clear patterns. These results provide a foundation upon which to design future therapeutic studies and identify a clear need for forming consensus approaches to treatment. *(J Pediatr 2015;166:970-7)*.

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, characterized by the formation of exudative airway casts,[1] greatly impact the length and quality of life of patients who undergo the Fontan procedure. Both of these conditions confer marked morbidity and high mortality after 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. The medical literature for plastic bronchitis also is limited and is composed almost entirely of case reports and case series.

The lack of data for PLE and plastic bronchitis is attributable largely to the rarity of these diseases; both occur in a relatively small percentage of patients undergoing Fontan.[2,6,7] Single centers do not have a sufficient number of patients to adequately power studies. Multicenter research, although 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 plastic bronchitis 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 plastic bronchitis risk factors, clinical course, and treatment.

BMI	Body mass index
IV	Intravenous
PHN	Pediatric Heart Network
PLE	Protein-losing enteropathy

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Methods

The methodology for this study has been previously published.[9] To summarize 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 plastic bronchitis. The survey was designed with the specific intent of conducting case-control analyses between patients with and without 1 or both of these complications. The survey was posted online and used 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.

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 plastic bronchitis. The survey was structured to encourage the participation of patients or parents of patients who had a Fontan procedure, regardless of whether they had been diagnosed with PLE or plastic bronchitis. 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 plastic bronchitis. The instrument was refined based on feedback received. The final survey consisted of 31 questions/items for patients with uncomplicated Fontan, 52 items for patients with PLE, 55 items for patients with plastic bronchitis, and 76 items for patients with both. A copy of the survey is available at: http://tinyurl.com/UmichFontanSurvey. The survey was linked to 2 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 via the use of 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.

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 birth date, surgical dates, and Fontan complication onset did not follow a feasible chronologic pattern also were 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 Analyses

Standard descriptive statistics outlined participant characteristics overall and were stratified by "uncomplicated," "PLE," "plastic bronchitis," and "both PLE and plastic bronchitis." We matched "uncomplicated" patients receiving Fontan 2:1 or 3:1 with complicated patients receiving Fontan (ie, those with a diagnosis of PLE or plastic bronchitis, respectively) by year of Fontan surgery. Postmatch examination of time from Fontan to study participation assured the control groups were not composed of a large percentage of patients <1 year from Fontan surgery who would be at greater risk of still developing PLE or plastic bronchitis thereby making poor controls. We then made group comparisons between PLE or plastic bronchitis and their matched controls in each participant characteristic by using χ^2 tests or Fisher exact tests, as appropriate, for categorical variables and Wilcoxon rank-sum tests for continuous variables. ORs and 95% CIs for being diagnosed with PLE or plastic bronchitis were also reported. For the validation with the existing Fontan cross-sectional study, we used 2-group comparisons including χ^2 test and *t*-test. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, North Carolina). A *P*-value <.05 was considered statistically significant.

Results

A total of 855 individuals with a Fontan palliation completed at least 1 survey question. Of these, a total of 671 respondents (78%), including 76 with PLE, 46 with plastic bronchitis, and 7 with both PLE and plastic bronchitis 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 I**. Additionally, 1.6% of patients reported having undergone heart transplantation after Fontan: 3 had PLE, 3 had plastic bronchitis, 1 had both PLE/plastic bronchitis, and 4 were non-PLE or patients with plastic bronchitis receiving Fontan.

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 after Fontan to diagnosis of PLE was 2.5 years (IQR 1-6). The large majority of patients with PLE 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 diagnosis of PLE 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 greatly among patients with PLE. Daily treatments reported by respondents included a high-protein diet (53%), enteral budesonide (36%), sildenafil (32%), prednisone (12%), intravenous (IV) or subcutaneous