Pediatric Heart Transplant Study

Example of a Successful Proposal

Proposal Title:
Outcomes of heart transplantation for patients with plastic bronchitis

Background:
Plastic bronchitis is a rare complication following single ventricle palliation with an estimated incidence between 4% and 14%.[1] Fontan-associated plastic bronchitis is also associated with significant morbidity and mortality. The median transplant-free survival following a diagnosis of plastic bronchitis is 8.3 years.[2] Therapies for plastic bronchitis are largely anecdotal, vary widely, and efficacy remains uncertain.[3,4] Heart transplantation has evolved as a potentially curative therapy for patients with plastic bronchitis following single ventricle palliation. A prior PHTS analysis of single ventricle patients with plastic bronchitis listed for heart transplant between 1993 and 2009 demonstrated resolution of plastic bronchitis in all patients who survived >30 days post-transplant.[5] While these results are promising, patients with plastic bronchitis also demonstrated a significant risk of early mortality with 30% dying within the first month. However, only 10 patients with plastic bronchitis underwent heart transplantation during the study period, limiting the analysis. Another single center study also suggested a risk for early mortality following heart transplantation in single ventricle patients with either plastic bronchitis or protein losing enteropathy, but only included 5 patients with the former diagnosis.[6] The etiology for the early mortality observed in this population is unclear. Despite concerns about early mortality, overall survival of Fontan patients following heart transplantation has improved in the recent era.[7] This improvement is likely multifactorial including advances in surgical techniques, immunosuppression strategies with an increased recognition of the role of antibodies, and perioperative care. Given advances in the management of this population,[8] it is unknown if the presence of plastic bronchitis remains a risk factor for early mortality in the current era.

Study rationale (include knowledge gaps and significance of this study):
The impact of plastic bronchitis on waitlist and post-transplant outcomes is unknown in the current era. Prior studies in this population have been limited by size with prior mentioned enrollment of 5 and 10 patients, respectively.[5,6] Based on a recent query of the PHTS database, there are 79 patients enrolled in PHTS with a diagnosis of plastic bronchitis, of which 57 have undergone heart transplantation. This represents a nearly 6-fold increase in sample size compared to prior publications and would comprise the largest reported cohort to date. A more recent PHTS analysis reviewed post-transplant outcomes in Fontan patients, but did not address plastic bronchitis specifically, despite constituting approximately 20% of the Fontan cohort.[7] This study will assess contemporary waitlist and post-transplant outcomes following heart transplantation in patients with plastic bronchitis.

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Hypothesis / Specific Aims:

Specific Aim 1: To assess the impact of Fontan-associated plastic bronchitis on waitlist mortality

> Hypothesis 1: Patients with plastic bronchitis will have longer waitlist times and inferior waitlist survival compared to Fontan patients listed for transplantation for other indications.

Specific Aim 2: To determine if the presence of plastic bronchitis is a risk factor for post-transplant morbidity and mortality following heart transplantation

> Hypothesis 2a: Given ongoing improvements in the perioperative management of patients with Fontan circulation undergoing heart transplantation, there will be no difference in post-transplant mortality following heart transplantation
>
> Hypothesis 2b: Patients with plastic bronchitis will have increased incidence of post-transplant morbidities including the need for mechanical circulatory support (ECMO or VAD), prolonged mechanical ventilation and longer ICU and hospital stays

Specific Aim 3: To compare hemodynamic profiles of Fontan patients with and without plastic bronchitis listed for transplantation.

> Hypothesis 3: Patients with plastic bronchitis will have more favorable hemodynamic profiles (lower EDP, lower Fontan pressure) compared to Fontan patients listed secondary to impaired ventricular function.

Data Elements to be used from the database:
- Demographic characteristics: Age at listing, age at transplant, sex, race (Demographics Form-1,2,3)
- Primary etiology: (Demographics Form-5b)
- Listing Date (Form 01-1)
- Main reason for listing (Form 01-4)
- Surgeries prior to listing – selected for Fontan procedure and date of surgery (Form 01-5)
- Status at listing (Form 01-6a.iv)
- Medical status at time of listing including inpatient, ICU, mechanical ventilation, inotropes, VAD or ECMO (Form 01-6b,6c,6f)
- Medical history – selected for respiratory and plastic bronchitis (Form 01-8a.xiii)
- Hemodynamics prior to listing including Fontan pressure, mean atrial pressure, pulmonary capillary wedge pressure, and/or ventricular end-diastolic pressure (Form 01-11b,11c,11e,11j)
- Date of transplant (Form 01T-1)
- Status at time of transplant (Form 01T-6a.iv)

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- Medical status at time of transplant including inpatient, ICU, mechanical ventilation, inotropes, VAD or ECMO (Form 01T-6b,6c,6f)
- Cardiopulmonary bypass time and donor ischemic time (Form 01T-16,17)
- Date and location of infection (Form 06-1,5)
- Date of death or retransplant (Form 09-15f,15g)
- Primary cause of death (Form 10-2)
- Patient removed from waitlist other than transplant or death including date and reason (Form 12-7,7a,7b)

Analysis Plan

Final analysis plan to be determined in conjunction with PHTS statisticians/DCC.

Patient population: Standardized data collection for plastic bronchitis began in 2010 and therefore this study will utilize PHTS data from 2010 – 2017. All patients with single ventricle anatomy status-post Fontan palliation will be included in the analysis. Patients will be stratified based on the presence or absence of plastic bronchitis with non-plastic bronchitis Fontan patients representing the control group. For the primary analysis, patients with protein losing enteropathy will be grouped with the non-plastic bronchitis group. As a secondary analysis, patients with protein losing enteropathy will be excluded from the non-plastic bronchitis group.

Aim 1: Baseline patient demographics at the time of listing will be compared between Fontan patients with and without plastic bronchitis. The chi-squared test will be used for categorical variables and the Student's t-test or Wilcoxon rank sum test will be used for continuous variables, as appropriate. Competing outcomes and Kaplan Meier analyses will be performed to assess the impact of plastic bronchitis on outcomes following listing. Multivariate analysis in the hazard function domain will be used to identify risk factors for waitlist mortality using a stepwise selection technique. The analysis will then be repeated after excluding patients with protein losing enteropathy.

Aim 2: Baseline patient demographics at the time of transplantation will be compared between Fontan patients with and without plastic bronchitis who survived to heart transplantation. Kaplan-Meier analysis will be performed with an event defined as post-transplant death or retransplantation. Patients will be censored at the time of an event or at last known follow-up. A Cox proportional hazard model will be constructed to assess for independent associations with post-transplant survival using a stepwise selection technique. The analysis will then be repeated after excluding patients with protein losing enteropathy.

Aim 3: Invasive hemodynamic profiles at the time of listing will be compared between Fontan patients with and without plastic bronchitis. Measurements will be compared using the Wilcoxon rank sum test and will include Fontan pressure, transpulmonary gradient, and

ventricular end-diastolic pressure. The comparisons will also be made after excluding patients with protein losing enteropathy.

References (limit to 10):

1. Caruthers RL, Kempa M, Loo A, Gulbransen E, Kelly E, Erickson SR, Hirsch JC, Schumacher KR, Stringer KA. Demographic characteristics and estimated prevalence of Fontan-associated plastic bronchitis. *Pediatr Cardiol.* 2013 Feb; 34(2): 256–261.
2. 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 Apr; 3(2).
3. Brooks K, Caruthers RL, Schumacher KR, Stringer KA. Pharmacotherapy challenges of Fontan-associated plastic bronchitis: a rare pediatric disease. *Pharmacotherapy*. 2013 Sep; 33(9): 922–934.
4. Schumacher KR, Stringer KA, Donohue JE, Yu S, Shaver A, Caruthers RL, Zikmund-Fisher BJ, Fifer C, Goldberg C, Russell MW. Fontan-associated protein-losing enteropathy and plastic bronchitis. *J Pediatr*. 2015 Apr; 166(4): 970–977.
5. Gossett J, Almond C, Kirk R, Zangwill S, Richmond M, Kantor P, Tresler M, Lenderman S, Naftel D, Matthews K, Pahl E. Outcomes of Cardiac Transplantation in Single Ventricle Patients with Plastic Bronchitis—a Multi-Center Report *J Am Coll Cardiol*. 2013 Mar 5; 61(9):985-6.
6. Griffiths ER, Kaza AK, Wyler von Ballmoos MC, Loyola H, Valente AM, Blume ED, del Nido P. Evaluating failing Fontans for heart transplantation: predictors of mortality. *Ann Thorac Surg*. 2009 Aug; 88(2):558-64.
7. Simpson KE, Pruitt E, Kirklin JK, Naftel DC, Singh RK, Edens RE, Barnes A, Canter CE. Fontan patient survival after pediatric heart transplantation has improved in the current era. *Ann Thorac Surg*. 103(4) 1315-1320.
8. Parent JJ, Darragh RK, Gossett JG, Ryan TD, Villa CR, Lorts A, Jefferies JL, Towbin JA, Chin C. Strategies to Prevent Cast Formation in Patients with Plastic Bronchitis Undergoing Heart Transplantation. *Pediatr Cardiol.* 2017 Jun; 38(5):1077-1079.

Proposal Timeline with Dates (from developing analysis to manuscript submission and including abstract deadline)

June - August – Data analysis
September 31st – Abstract completion
October 31st (or by deadline if earlier) - Submit abstract to 2020 ISHLT Annual Meeting and Scientific Sessions
July-October – Draft, revise and finish manuscript
April 22-25th, 2020 – Present at ISHLT Annual Meeting and Scientific Sessions in Montreal, Canada
April, 2020 – Complete manuscript and submit to Journal of Heart and Lung Transplantation