PHTS Study Proposal Application

Title: Bacterial infections following pediatric heart transplantation: Epidemiology, risk factors, and outcomes

Background: Despite improvements in patient outcomes among heart transplant recipients in recent decades, infections remain an important cause of morbidity and mortality. In pediatric heart transplant recipients, infections account for 16% of deaths in the first year after transplant, and they remain among the top 4 causes of death in subsequent years. The most common etiologies of these infections are bacteria, which affect up to half of all pediatric heart transplant recipients. Despite the high incidence of bacterial infections in this patient population, there is limited data describing the epidemiology, risk factors, and patient outcomes. Most previous studies evaluating the epidemiology of infectious complications in heart transplant recipients have been limited to adult data or to single centers with small patient numbers. A comprehensive analysis of the Pediatric Heart Transplant Study Group for infectious complications was last performed in 1997, but changes in patient care and risk factors have occurred since that time. These include the evolution of immunosuppressive regimens, the introduction of the pneumococcal conjugate and polysaccharide vaccines, and the emergence of multi-drug resistant pathogens. Understanding the current incidence and types of serious bacterial infections, their risk factors, and clinical outcomes may help illuminate strategies to better prevent and treat these infections in the future.

Risk for bacterial infections is highest in the early post-transplantation period (0 to 30 days after transplant) in association with surgical complications and prolonged hospitalization. These early infections are most commonly hospital-acquired pneumonias, catheter-related bloodstream infections, surgical-site infections, urinary tract infections, and Clostridium difficile colitis. Nosocomially acquired bacteria are the most common causative pathogens, and the incidence of multi-drug resistant infections is increasing. In the intermediate post-transplantation period (31-180 days), risk of nosocomial infections decreases, and classic opportunistic infections, including Nocardia and Legionella, emerge. In the late post-transplantation period (> 180 days), common community acquired bacterial pathogens, including Streptococcus pneumoniae, predominate.

Risk factors for bacterial infection include factors associated with the transplant surgery and prolonged hospitalization, in addition to the risks of long-term immunosuppressive regimens. There is evidence that infant transplant recipients are at increased risk of serious bacterial infections and chronic or recurrent bacterial infections. This may be because infant recipients have not yet developed protective antibodies against common bacterial and vaccine preventable pathogens prior to transplantation. Additionally, the effects of chronic immunosuppressive regimens on the developing immune system are incompletely understood. These factors may predispose infants and young children to bacterial infections in both the
early and late post-transplantation period. Understanding these patient risk factors may assist
in decision making regarding preventative and therapeutic management.

**Objectives:**
The primary objectives of this study are to describe the epidemiology, risk factors, and
outcomes of bacterial infections in pediatric heart transplant recipients.

**Specific Aim #1:**
To describe the epidemiology of bacterial infections in pediatric heart transplant recipients in
terms of their incidence, sites of infection, and bacterial etiologies. Infections will be stratified
by the type of causative pathogen: (1) infections associated with hospitalization or surgery; (2)
opportunistic infections; and (3) common bacterial infections. The incidence of invasive
*Streptococcus pneumoniae* over time will be specifically analyzed to describe the trend of this
important bacterial pathogen in pediatric heart transplant recipients before and after the
introduction of pneumococcal conjugate and polysaccharide vaccines.

**Specific Aim #2:**
To describe risk factors associated with acquisition of bacterial infections, including patient
demographic characteristics, age at time of transplantation, age at time of infection, timing of
infection after transplantation, immunosuppressive regimens, and pre- and post-transplant co-
morbidities and procedures.

**Specific Aim #3:**
To describe outcomes of invasive bacterial infections in terms of recurrence, chronicity,
mortality, and long-term morbidity.

**Data Collection:**

**Study Population:**
All eligible pediatric (≤ 18 years of age) patients transplanted between 1993 and 2013 and
enrolled in the Pediatric Heart Transplant Study database will be included for analysis.

**Design:**
The study will be a retrospective cohort analysis of the Pediatric Heart Transplant Study
database of recipients transplanted at ≤ 18 years of age.

**Methods:**
The PHTS database will be queried for all transplant recipients during the study period:
- Patient age at transplant (Form 01)
- Demographic characteristics: Gender, race, primary insurance (Form 01)
- Medical co-morbidities (Form 01)
- Etiology of heart disease (Form 01)
Cardiac surgical history (Form 01)
- Status and support at transplant (Form 01T)
- Initial immunosuppression and antibiotics (Form 03)
- Age at infection (Form 06)
- Date of infection (Form 06)
- Timing of infection after transplant (Form 06)
- Drug therapy at time of infection (antibiotic prophylaxis, immunosuppressive medications) (Form 06)
- Name of bacterial organism (Form 06)
- Location of infection (Form 06)
- Presence of co-infections (Form 06)
- Therapy for infection (Form 06)
- Surgical interventions (Form 06)
- Outcomes: resolution, long-term sequelae, or death (Form 06)

Analysis:
The primary outcome measure will be the incidence of bacterial infections. Infections which required IV therapy or life threatening infections which required oral therapy will be included if a bacterial etiology was identified. The data will be examined using standard descriptive statistics, including means, standard deviations, and standard errors. Standard Kaplan-Meier and parametric analyses will be used for survival analysis. Multivariate analysis in the hazard-function domain will be used to identify risk factors for death. The hazard curve will be a mathematical function estimated by the data to depict instantaneous risk of first bacterial infection. Variables entered into the multivariable risk factor analysis for death will include demographic characteristics, underlying cardiac condition, medical co-morbidities, surgical history, listing status at time of transplant, the need for vasopressors or inotropes at the time of transplant, mechanical ventilation, the need for ECMO, use of VAD prior to transplant, timing of infection after transplantation, name of bacterial organism, location of infection, presence of co-infections, immunosuppressant medications at time of infection, and therapy for infection. Final statistical analysis will be performed in collaboration with PHTS statisticians.

References: