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A multi-institutional evaluation of antibody-mediated rejection utilizing the Pediatric Heart Transplant Study database: Incidence, therapies and outcomes

Philip T. Thrush, MD,[a] Elfriede Pahl, MD,[a] David C. Naftel, PhD,[b] Elizabeth Pruitt, MSPH,[b] Melanie D. Everitt, MD,[c] Heather Missler, RN, BSN,[d] Steven Zangwill, MD,[e] Michael Burch, MD,[f] Timothy M. Hoffman, MD,[g] Ryan Butts, MD,[h] and William T. Mahle, MD[i]

From the [a]Department of Pediatrics, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois, USA; [b]Department of Cardiothoracic Surgery, University of Alabama at Birmingham, Birmingham, Alabama, USA; [c]Department of Pediatric Cardiology, Children's Hospital Colorado, Aurora, Colorado, USA; [d]Department of Pediatrics, Nationwide Children's Hospital, Columbus, Ohio, USA; [e]Department of Cardiology, Phoenix Children's Hospital, Phoenix, Arizona, USA; [f]Cardiorespiratory Division, Great Ormond Street Hospital for Children, London, UK; [g]Department of Pediatrics, University of North Carolina Children's Hospital, Chapel Hill, North Carolina, USA; [h]Department of Pediatrics, Medical University of South Carolina, Charleston, South Carolina, USA; and the [i]Department of Pediatrics, Children's Healthcare of Atlanta, Atlanta, Georgia, USA.

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BACKGROUND: Current knowledge of antibody-mediated rejection (AMR) after heart transplantation (HT) stems largely from adult data. Using the Pediatric Heart Transplant Study (PHTS) database, we report the incidence of AMR, describe treatment, and evaluate outcomes for treated AMR in children after HT.

METHODS: We queried the PHTS database for patients <18 years of age undergoing primary HT between January 2010 and December 2014. An AMR episode was defined as either a biopsy consistent with pathologic AMR or a rejection event based on immunotherapy augmentation directed against antibody production. Biopsy data, treatment strategies and survival were analyzed.

RESULTS: An episode of AMR was identified in 179 of 1,596 (11%) HT recipients and in 246 of 705 (35%) rejection episodes. AMR was diagnosed by biopsy in 182 of 246 episodes and by immunotherapy in 64 of 179 episodes. Mixed rejection was identified in 179. Freedom from AMR was 88% and 82% at 1 and 3 years, respectively. AMR therapies included intravenous immunoglobulin (IVIg) (58%), plasmapheresis (40%), rituximab (40%), bortezomib (11%) and eculizumab (0.4%). The most commonly used combination therapies included IVIg/plasmapheresis/rituximab (13%). Thirty-three patients (16%) died after developing AMR. Patient and graft survival were lower for the AMR^+ group. One- and 3-year survival after initial AMR diagnosis was 88% and 77%, respectively.

CONCLUSIONS: In his study we report the largest experience of AMR in pediatric HT recipients. AMR was common and often occurred concurrently with acute cellular rejection. There is wide variability in the treatment of AMR. Short-term patient and graft outcomes were worse for those with treated AMR.

Reprint requests: Philip T. Thrush, MD, Ann & Robert H. Lurie Children's Hospital of Chicago, 225 East Chicago Avenue, Box 21, Chicago, IL 60611. Telephone: +312-227-4100. Fax: +312-227-9640.
E-mail address: pthrush@luriechildrens.org

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Antibody-mediated rejection (AMR) was first described by Herskowitz et al,[1] and its occurrence has become a major component of post-transplant surveillance. The biopsy diagnosis of AMR has a significant impact on both patient and graft survival.[2] Identified risk factors for AMR include female gender (recipient), multiparity, blood transfusion (particularly platelets), positive peri-operative T-cell cross-match, allosensitization, ventricular assist device and previous surgery for congenital heart disease (CHD), especially that involving homograft tissue.[3–5]

AMR has been reported in up to 20% of patients early after heart transplantation (HT), and is also a significant component of late rejection, with 1 study reporting 25% of cases occurring >1 year after HT.[3,6] Pediatric studies have demonstrated an association between AMR, cardiac allograft vasculopathy (CAV) and graft failure; however, there has been no large-scale analysis of the impact of patient survival after AMR, nor is it known how AMR compares with acute cellular rejection (ACR) *vis-à-vis* patient or graft survival.[4,7,8] Furthermore, there are few data regarding therapies employed to manage AMR in children. Therefore, we queried a multicenter HT registry to: (1) describe the incidence of AMR after pediatric HT; (2) assess the contemporary management of AMR; and (3) evaluate the short-term outcomes of patients treated for AMR.

Methods

The Pediatric Heart Transplant Study (PHTS) is a multi-institutional database that receives data from 52 pediatric transplantation centers. The database is prospective and event-driven and receives submissions at discrete time-points, such as time of listing, transplantation, annually and at death, and when specific events occur, including use of mechanical support, rejection infection and post-transplant lymphoproliferative disease (PTLD). Local institutional review board approval is maintained at each institution. The central database is maintained at the University of Alabama at Birmingham, where computer entry and data verification occur. We queried the PHTS database for all patients <18 years of age who underwent a primary HT between January 1, 2010 and December 31, 2014. These dates were chosen due to revisions in the data collection forms in January 2010, which allowed for capture of AMR events.

Definition of AMR

The PHTS defines rejection as "an event leading to augmentation of immunotherapy" and the appropriate form is submitted to the PHTS when an event matching this definition occurs. A histologic diagnosis is not required to meet the end-point definition of rejection. Although this definition does not differentiate between ACR and AMR, the dedicated *Rejection* form collects data to differentiate ACR and AMR (e.g., if complement staining is performed, then these data are collected). Although AMR grading using the proposed 2011 International Society for Heart and Lung Transplantation (ISHLT) grading system may be reported, for the purpose of database entry, AMR is identified as either present or absent regardless of AMR grade reported. For this study, an AMR episode was defined as a treated episode of rejection with either: (1) a biopsy with histology and/or complement staining consistent with pathologic AMR; or (2) a rejection event treated with immunotherapy augmentation directed against antibody production. For example, a subject with a rejection event that was treated with rituximab but with no data regarding C4d staining was presumed to have AMR.

Patient data

Patient-specific variables collected included age, gender, race, diagnosis, ABO compatibility at time of transplant, presence of mechanical circulatory support (MCS), panel-reactive antibody (PRA), retrospective crossmatch data, induction immunotherapy, date of HT, date of rejection episode and treatments. AMR-specific therapies, including intravenous immunoglobulin (IVIg), rituximab, plasmapheresis, bortezomib and eculizumab, were identified for each treatment of AMR.

Data and statistical analysis

Data collection, data checking and verification were performed according to PHTS standard methods at the University of Alabama. Continuous variables were divided into categories and analyzed as categorical variables. Descriptive statistics are presented as frequencies and percentages. Baseline characteristics were compared using chi-square tests. The criterion for statistical significance was set at $\alpha = 0.05$. Standard Kaplan–Meier non-parametric curves were used to demonstrate time to first rejection, time to first infection after rejection and survival after rejection. Cox proportional hazards models identified independent risk factors for AMR. Hazard ratios (HRs) are presented with 95% confidence intervals (CIs). All statistical analyses were performed with SAS version 9.4 (SAS Institute, Inc., Cary, NC) software.

Results

Incidence of rejection

The PHTS database identified 1,596 patients who underwent primary HT between January 1, 2010 and December 31, 2014. Of these patients, 480 (30%) experienced 705 episodes of rejection. AMR was reported in 179 (11%) patients and accounted for 246 of the 705 (35%) rejection episodes. Demographics and cohort characteristics are presented in Table 1. AMR was diagnosed by biopsy in 182 episodes, by antibody-directed therapy in 47 episodes with a negative biopsy, and in 17 episodes by antibody-directed therapy in which no biopsy was performed. Of those patients reported to have rejection and identified AMR by biopsy, 125 of 182 (69%) were treated for AMR with therapies beyond corticosteroids. Of those with AMR identified by treatment or biopsy, 121 episodes had concomitant ACR Grade 1R or greater. Of the 246 episodes of reported AMR, 24 were reported in 2010, 40 were reported in 2011, 51 were reported in 2012, 57 were reported in 2013 and 74 were reported in 2014.