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Decline in rejection in the first year after pediatric cardiac transplantation: A multi-institutional study

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BACKGROUND: Rejection is a major cause of morbidity and mortality after pediatric heart transplantation (HTx). Survival after pediatric HTx has improved over time, but whether there has been an era-related improvement in the occurrence of allograft rejection is unknown.

METHODS: The Pediatric Heart Transplant Study (PHTS) database was queried for patients who underwent HTx from January 1993 to December 2005 to determine the incidence of rejection and identify factors associated with the first episode of rejection in the first year after HTx.

RESULTS: Data were reviewed in 1,852 patients from 36 centers. The incidence of rejection declined over 13 years at a rate of -2.58 ± 0.41 ($p < 0.001$) from approximately 60% to 40% ($p < 0.001$). The mean number of episodes of rejection also significantly fell at a rate of -0.05 ± 0.01 per patient/year from 1.19 to 0.66 ($p < 0.001$). The incidence of rejection with hemodynamic compromise and death from rejection did not change. Multivariate analysis for the risk of a first rejection episode demonstrated decreased risk of rejection with later year of HTx (odds ratio [OR], 0.88; 95% confidence interval [CI], 0.85–0.91; $p < 0.001$) and use of mechanical support (OR, 0.65; 95% CI, 0.42–0.99; $p = 0.046$). Increased risk of rejection was associated with positive donor-specific crossmatch (OR, 1.85; 95% CI, 1.18–2.88; $p = 0.007$) and older recipient age (OR, 1.05; 95% CI, 1.02–1.07; $p < 0.001$).

CONCLUSIONS: Although the overall incidence and prevalence of rejection has substantially decreased over time in pediatric HTx recipients in the first year after HTx, the rate of rejection with hemodynamic compromise or death from rejection remains unchanged.

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Rejection is one of the major causes of morbidity and mortality after heart transplantation (HTx).[1,2] Survival is decreased in pediatric HTx patients who experience an episode of rejection during the first year after HTx,[3] and most acute rejection episodes occur in the first year.[4] Fur-

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thermore, rejection in the first year after HTx predicts subsequent rejection, which in turn is associated with increased death.[5] In the pediatric population, overall mortality after HTx has improved with time,[3,6] but whether a similar era effect exists for rejection is unknown. The primary aim of this study was to investigate in a large multicenter cohort whether rejection incidence, frequency, and mortality in this critical first year after pediatric HTx has improved in recent years. A secondary aim was to assess which risk factors were associated with an initial episode of rejection developing in the first year after HTx.

Methods

The Pediatric Heart Transplant Study (PHTS) is a multiinstitutional database that acquires data from 36 pediatric transplantation centers (Appendix). The PHTS is a prospective, event-driven database that receives submissions both at discrete time-points (ie, at time of listing, transplantation, annually, and at death) as well as on the occurrence of specific events such as rejection, post-transplantation lymphoproliferative disorder (PTLD), and infection. Local Investigational Review Board approval is maintained at each institution, and the central database is maintained at the University of Alabama at Birmingham, where computer entry and data verification are performed. We queried the PHTS database for all patients who underwent HTx from January 1993 to December 2005. This analysis was performed on patient data ending December 2006 so that all study patients would have a full 12 months of observation. Patients who died within 1 year of HTx without an episode of rejection were excluded, but we also performed a secondary "worst-case" analysis in which we made the assumption that all of these patients had rejection.

Definition of rejection

The primary outcome measure for this study was rejection in the first year after HTx. The PHTS defines rejection as "an event leading to augmentation of immunotherapy," and an episode of rejection is therefore said to have occurred if an event matching this definition is reported to the PHTS database on the dedicated rejection form. This definition has been extensively used in numerous publications in both the pediatric and adult population.[4,5,7–11] This definition does not attempt to differentiate between cellular, antibody-mediated (AMR), or mixed etiologies of rejection.

The basis for the diagnosis of rejection (clinical grounds, echocardiography, or biopsy specimen with International Society for Heart and Lung Transplantation [ISHLT] grade), the presence of associated hemodynamic compromise (HC), and death from the episode are recorded on the submitted forms. Biopsy specimens analyzed before the 2005 revised ISHLT biopsy system were converted to the revised scale as follows: grade 0R, no rejection; grade 1R (previous grades 1A, 1B, and 2), grade 2R (previous grade 3A), and grade 3R (previous grades 3B and 4).[12,13] Deaths that occur in patients followed up at participating PHTS centers are reported through a dedicated form. The center selects a sole primary cause of death and patients whose primary cause of death was reported as rejection were considered as having had death from rejection.

Patient variables

A number of patient-specific variables were collected to assess their association with rejection in the first year after HTx. These variables included age at HTx, gender, race, underlying disease (cardiomyopathy vs congenital heart disease), number of sternotomies and/or thoracotomies, use of mechanical support (extracorporeal membrane oxygenation or ventricular assist device) at time of transplant, evidence of past cytomegalovirus infection, pre-sensitization (any panel reactive antibody [PRA] level $> 10\%$), donor ischemic time, positive donor/recipient crossmatch, use of induction therapy after HTx, use of cyclosporine, tacrolimus, azathioprine, and/or mycophenolate mofetil as initial immunosuppression, and use of steroids beyond 30 days after HTx.

Data analysis

Data collection, data checking, and verification were performed according to PHTS standard methods by the University of Alabama at Birmingham. Data analyses were conducted at Washington University in St. Louis. Continuous variables were reported as mean $\pm$ standard deviation, and categoric variables were reported as the frequency and percentage. Linear regressions were used to determine whether any changes occurred from 1993 to 2005 in patient variables, in methods to diagnose rejection (clinical impression, echocardiography, or endomyocardial biopsy), and the in the outcome measures the incidence of rejection within the first year after HTx, the incidence of death from rejection, the incidence of rejection with HC, and the number of rejection episodes in the first year after HTx per patient.

Statistics

Risk factors associated with the initial rejection episode within the first year after HTx were explored initially using univariate logistic regression among patient variables. We performed multivariate logistic regression among the variables with a value of $p < 0.1$ in the univariate logistic regressions. Stepwise procedures were used to identify the specific factors that were independently associated with rejection within the first year after HTx. A value of $p < 0.05$ was used to determine significance, and odds ratios (OR) are presented with their 95% confidence intervals (CI). All analyses were performed with SAS 9 software (SAS institute, Cary, NC).