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Practice variability in pediatric heart transplantation: Opportunities for collaboration

Aecha Marion Ybarra

Chesney Castleberry

Review Article

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Aecha Marion Ybarra, Chesney Castleberry

Department of Pediatric Cardiology, Washington University in St. Louis, School of Medicine, St. Louis, MO, USA

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Correspondence to: Chesney Castleberry, MD. Pediatric and Congenital Cardiology Associates of Austin, 4314 Medical Parkway, Ste 200, Austin, TX 78756, USA. Email: Chesney_Castleberry@mednax.com.

Abstract: The pediatric heart transplant population continues to grow and more centers are now providing advanced heart failure and transplant services. Though more patients are surviving after transplant, pediatric center protocols have remained relatively unchanged with limited research to guide protocol optimization. The authors explore recent literature reviewing the impact of the different approaches to pre and post-transplant care and as well as the impact these variations have on the field and future directions.

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The number of pediatric heart transplants worldwide has continued to increase over time and is now around 600–700 transplants per year (1). Despite this apparent increase, the number of centers performing pediatric heart transplants has remained stable since the late 1990s, with the majority of centers reporting an average of 1–4 transplants per year; while the remaining centers perform 5–9 or over ten transplants per year. Current survival is improving, with around 90% of patients achieving the 1-year mark, however current treatment practices are not standardized (2).

A recent analysis of the organ procurement ad transplantation network (OPTN) revealed that there are significant differences in post-transplant patient and graft survival among currently active pediatric heart transplant centers in the United States (3). It was suggested that annual transplant volumes could somewhat explain these differences and short term performances, however, the analysis was limited to the information provided by the registry, which poorly defines center practices. There is limited knowledge about the uniformity of clinical practices in the pediatric heart transplant population to explain outcome variability.

Variability in clinical practices among institutions has been associated with inconsistent outcomes across multiple disease processes, with improvement seen when adherent to standardized clinical practices (4-7). Evaluation of protocols has become an important topic in all facets of medicine, including pediatric heart transplant (7-11). Several studies have attempted to identify variations in practices and analyze their differences to reach a consensus on best practices within pediatric heart transplant (9). In pediatric heart transplantation, clinical protocols tend to be center-specific or experienced-based and extrapolated from less than ideal sources (10-12). Evidence-based guidelines based on clinical trials are mainly lacking.

Center variability also impedes the ability to perform quality clinical outcomes research using registries as a portion of the practice variations that could influence outcomes are not always collected. An example of this is the type and duration of CMV prophylaxis which has been shown to influence coronary allograft vasculopathy (CAV) outcomes (13-15). Other prophylaxis CAV medication use, maintenance immunosuppression targets, and treatment of donor specific antibodies are all other potential protocols that can influence clinical outcomes and are largely missing in registry analysis.

Endomyocardial biopsy (EMB) remains the mainstay for the diagnosis of rejection; however, there is considerable variability in the frequency of monitoring amongst transplant programs, particularly within the first year post-heart transplant (16). While there has been a decrease in the incidence of rejection in the more recent era of immunosuppression, there has been no significant change in the frequency of surveillance EMB over time (11). This may be due to the lack of information regarding the impact of changes in practices on outcomes, particularly in pediatrics. Though various non-invasive tests have been developed for evaluating for rejection, including advanced echocardiography, intramyocardial electrography, and gene expressions, these techniques are more frequently being used in the adult population and have yet to be validated in the pediatric population. This may suggest that better-designed studies correlating standardized rejection surveillance practices with clinical outcomes are needed and standardization could decrease exposure of the population to invasive procedures.

Steroids once were the mainstay of immunosuppressive therapies for solid organ transplantation, however, have significant side effects including Cushingoid facies, cataracts, obesity, hyperlipidemia, osteopenia, avascular bone necrosis, and severe growth retardation (12). Over time, programs have adapted steroid tapers or alternative steroid therapies, which have minimized the impact of secondary effects. However, hypertension, obesity, diabetes, and growth retardation remain common side effects. In a recent survey, most centers used a corticosteroid taper postoperatively, with the most common taper of 2–6 months and a small percentage of centers using a steroid-free protocol (1/28, 4%) (9). Database analyses and studies are still investigating the practicality of a steroid-free protocol.

Despite the challenges of reliable data for decision making, there is a high amount of uniformity in most areas of clinical practice (9). Previous surveys indicated consistency among programs with regards to infection prophylaxis with most centers reporting similar protocols for fungal, CMV, and pneumocystis carinii (>80%). There was also strong agreement with regards to maintenance immunosuppression with most centers (>85%) prescribing tacrolimus and mycophenolate mofetil at the time of discharge (9).

Fortunately, there appears to be a willingness to change clinical practices as part of an effort to form a single protocol (9). Recently, a randomized control trial was initiated using a uniform post-transplant protocol and includes over 35 pediatric heart transplant centers (17). This trial (TEAM-MATE) also standardizes two maintenance immunosuppression regimes, including the therapeutically monitored tacrolimus and everolimus. There is additional interest within the pediatric heart transplant community to expand on this effort with other aspects of post-transplant care through loose collaboration between centers with similar protocols. Though it is unlikely that all practices can be standardized through randomized control trials given the size of the population and cost of funding, center cooperation is a potential tool to broadening the understanding of the impact of different clinical pathways on outcomes.

While there exist such variations among pediatric heart transplant centers, the majority of the major components of clinical practice protocols are similar. To adequately power an RCT in pediatric heart transplantation, study design must minimize potential confounding due to variation in clinical practice patterns. There have been several initiatives to standardize practices by the Pediatric Heart Transplant Society, however, expecting all centers to agree on one protocol may not be feasible. While we have made significant gains in pediatric heart transplant outcomes, a movement towards a standard protocol to refine clinical outcomes research is vital to further improvement of long term outcomes in pediatric heart transplantation.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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