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Guest Editorial

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Paediatric heart transplantation: life-saving but not yet a cure

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Abstract

In the 1980s, heart transplantation was the first successful treatment for infants born with hypoplastic left heart syndrome. Infants who have required heart transplantation benefit from immunologic "advantages," including long-term survival free from cardiac allograft vasculopathy. Currently ~ 90% of children undergoing a heart transplant are reaching their first-year anniversary and the clinical practices of paediatric heart transplantation have dramatically improved. These successes are largely attributed to research sponsored by the Pediatric Heart Transplant Study Group, the International Society of Heart and Lung Transplantation and, more recently, the Non-profits Enduring Hearts and Additional Ventures. Despite these successes, the field is challenged to increase progress to achieve long-term survival into adulthood. The wait-list mortality, especially among infants, is unacceptably high often leading to palliative measures that can increase post-transplant mortality. Cardiac allograft vasculopathy remains a major cause for progressive graft loss of function and sudden death. The relative tolerance seen in immature recipients has not been translated to modifying older recipients' post-transplant outcomes. The modifiable cause(s) for the increased risks of transplantation in children of different ethnicities and races require definition. Addressing these challenges faces the reality that for-profit research favours funding adult recipients, with ~ 10-fold greater numbers, and their more modest longevity goals. Advocacy for funding "incentives" such as the Orphan Drug rules in the United States and upholding principles of equity and inclusion are critical to addressing the challenges of paediatric heart transplant recipients worldwide.

Section 1. The development of paediatric heart transplantation: history and lessons learned

History

The first reported infant heart transplant was performed in 1967. The recipient survived less than a day.[1] Infant heart transplantation for inoperable CHD was first performed later in the 1980s as definitive therapy for hypoplastic left heart syndrome which at that time was uniformly lethal. The first report detailed the orthotopic xenotransplantation of an infant with hypoplastic left heart syndrome performed in 1985 by Bailey et al at Loma Linda.[2,3] Although this infant only lived 20 days before succumbing to the immunological sequelae of xenotransplantation, Bailey et al subsequently published their successful orthotopic cardiac transplantation in 11 of 14 infants using donated human hearts.[4] The complexities of pre- and post-transplant care of infants with unpalliated hypoplastic left heart syndrome required the development of many innovative pre- and post-transplant management approaches.[5] For example, non-invasive monitoring for rejection was developed for surveillance of transplanted infants.[6,7] Of the original cohort of infants with hypoplastic left heart syndrome undergoing primary transplant, survival at 10 and 25 years was 73.9% and 55.8%, respectively. The oldest survivor is now 37 years old with his first graft.(RC personal communication) At 20 years, freedom from allograft vasculopathy (Fig. 1) and lymphoproliferative disease was 72.0% and 81.9%, respectively.[8]

Lessons learned/future research objectives in need of more funded research

Heart transplantation was the first successful treatment for infants born with hypoplastic left heart syndrome. The question remains whether primary heart transplantation or staged palliation is superior for infants born with hypoplastic left heart syndrome.[9] Following transplantation, cardiac anatomy and function are typically normal, though with the long-term risks of rejection and dependency on immunosuppression.[10] Following staged palliation

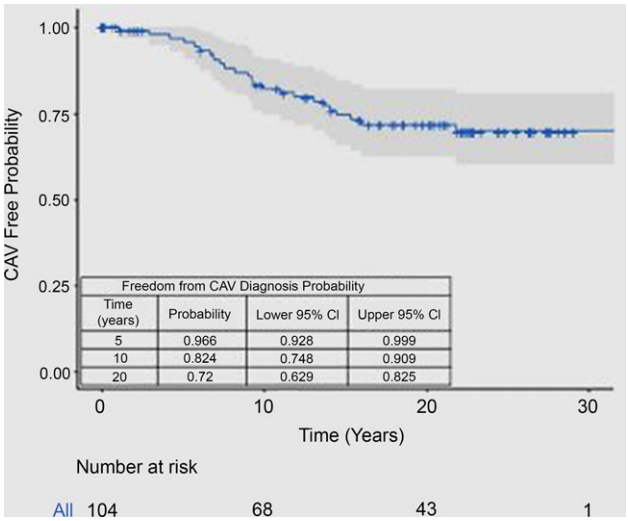

Figure 1. Freedom from cardiac allograft vasculopathy.[8]

cardiovascular physiology remains abnormal, with potential development of liver dysfunction, plastic bronchitis, and protein-losing enteropathy and typically life-long need for medications and re-interventions. Post-transplant survival of younger children (median age was 3.8 years (interquartile range, 0.6–11.5) with hypoplastic left heart syndrome before or after staged palliation was similar in an early report.[11] Both staged palliation and primary transplantation of infants carry similar (~20%) possibilities requiring either primary or a second heart transplant.[11] Based on survival and quality of life in current heart transplant management and assuming sufficient donor availability, primary heart transplantation could be a preferred option for higher-risk single-ventricle patients.

Infants who have undergone heart transplantation benefit from immunologic "advantages."[12,13] These benefits include less frequent acute rejection[14] and longer cardiac allograft vasculopathy-free survival (Fig. 1).[8,14] Long-term absence of antibodies against the donor blood group illustrates a feature of graft "acceptance" uniquely associated with the immature immune system.[12,15,16] Reduced intensity of immunosuppression has been successful in younger patients, as their risks for adverse outcomes have been shown to be higher for infection than rejection.[10] That said, immunosuppression protocols are still somewhat idiosyncratic. Only one multi-centre randomised trial in paediatric heart transplantation has compared two different immunosuppression protocols, and the detailed results from this trial have not yet been published.[17] Clearly, the unique immune system of infant recipients has many opportunities for the personalisation of the intensity and scope of their immunosuppression.[14,18]

Section 2. Contributions of Pediatric Heart Transplant Study Group, International Society for Heart and Lung Transplantation and later Enduring Hearts and Additional Ventures in growing the science and improving the practices of paediatric heart transplantation

Contributors to improving organ utilisation, longevity, and quality of lives for children requiring heart transplantation have predominantly been the Pediatric Heart Transplant Study Group since 1992, Enduring Hearts since 2015 and their collaborations with the International Society of Heart and Lung Transplantation since 1981, the American Heart Association and Additional Ventures (AV). Under the direction of Jim Kirklin, MD, and David Naftel, PhD, Pediatric Heart Transplant Study Group developed a collaborative structure and now most paediatric heart transplant programmes in the United States, and many from other countries, are contributing data to its registry. The Pediatric Heart Transplant Study Group now has 62 participating paediatric heart transplant centres across the globe and collected data on over 12,000 listings and almost 9,000 paediatric heart transplant recipients. The Pediatric Heart Transplant Study Group's goal has been for paediatric heart transplant centres to collaborate to identify common and unique issues related to the care of paediatric heart transplant recipients. Through this unique and successfully implemented collaborative structure developed by Pediatric Heart Transplant Study Group, a generation of data-directed paediatric transplant cardiologists have generated over 140 abstract presentations and over 100 peer-reviewed articles. In 2010, Pediatric Heart Transplant Study Group created a non-profit foundation to fund research based on its well-curated database.

Enduring Hearts was founded in 2015 by the family of a paediatric heart transplant recipient to fund prospective research studies to improve graft longevity. Enduring Hearts is the only non-profit organisation dedicated solely to funding research for children with heart transplants. Since its inception, Enduring Hearts has embraced the collaborative spirit of Pediatric Heart Transplant Study Group and partnered also with the International Society for Heart and Lung Transplantation, the American Heart Association and Additional Ventures. Together, Enduring Hearts has invested ~ 10 million dollars to fund 60 investigator-initiated research projects. The impact(s) of these funded studies towards improving the early diagnosis of, and treatment for, rejection that has been reported in the most recent era[19] remains to be studied with advanced analytics. Other contributions have included novel technology applications, immune system modulation, and increased donor heart availability and quality, improving adolescent medication compliance. More recently, Enduring Hearts has initiated Innovative Challenge Grants and Longevity Awards, with International Society for Heart and Lung Transplantation, and Translational Research Awards, with American Heart Association and Additional Ventures, incentivising the rapid translation of investigator-identified preliminary evidence into clinical trials for paediatric heart transplant recipients. Recognising the critical role of families in the outcomes following paediatric heart transplantation particularly during the first year after heart transplantation, Enduring Hearts is also funding a trial programme that provides financial support for families in the first-year post-transplant.

Section 3. The challenge for paediatric heart transplantation: increase the pace of progress in discovery and innovation

The contributions of Pediatric Heart Transplant Study Group, Enduring Hearts, ISHLT, and Additional Ventures in growing the science and improving the practices of paediatric heart transplantation have likely contributed to the fact that currently ~ 90% of children now undergoing a heart transplant are reaching their first-year anniversary. Despite these encouraging outcomes after paediatric heart transplantation in the current era,[20] many challenges of long-term care and survival require additional clinical studies and overcoming barriers to necessary funding resources. Several examples unique to paediatric heart

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transplantation listed below underscore barriers as well as opportunities to accelerate the pace of progress in discovery and innovation. A common barrier is funding. The limited numbers of paediatric recipients at each centre often requires multi-institutional studies and trials to provide significant evidence. While an extreme need, children with severe heart disease represent a negligible market segment. Accordingly, industry investments have favoured adult applications, with higher financial return compared to that anticipated from the much smaller and more diverse paediatric population.

First, the ongoing high wait-list mortality, especially among infants, has highlighted the need to expand the donor pool. Even though expanding donor opportunities with ABO-incompatible transplants is well established,[21] further funded studies will help define age cut-offs and antibody titres consistent with safe transplantation. These studies may also allow immune manipulation permitting expansion of ABO-incompatible transplantation into adulthood as routinely performed in kidney transplant[22] and successfully in selected adult heart transplant cases.[23] To reduce the barriers of ischaemic time and geography, more optimal conditions for preserving and restoring function of paediatric donor hearts are needed.[24,25] With genetic modifications, porcine heart xenotransplantation in neonates and infants with complex CHD, particularly univentricular circulation, is a potential therapeutic option.[26]

Second, cardiac allograft vasculopathy and late graft failure remain a major cause for progressive loss of graft function and sudden death after paediatric heart transplantation. Funded research focused on the prevention, early detection, and effective treatment of cardiac allograft vasculopathy in paediatric heart transplantation recipients should significantly improve long-term survival. The causes, course, and responses to medical interventions for cardiac allograft vasculopathy cannot simply be extrapolated from adult studies.[20,27] In contrast to the "accelerated atherosclerosis" which often affects adult recipients, in the paediatric setting other potentially modifiable immune-mediated endothelial cell effects are more likely drivers of cardiac allograft vasculopathy. These fundamental pathophysiologic differences may, in part, explain why statin therapy has a beneficial effect in ameliorating cardiac allograft vasculopathy in adult recipients,[28] but of limited benefit in children.[29] The potential for loss of vascular access after repeated endomyocardial biopsies and coronary angiograms is particularly problematic after paediatric heart transplantation.[30] The imperative for effective and non-invasive monitoring after paediatric heart transplantation that is predictive for rejection/cardiac allograft vasculopathy clearly merits further research funding.[31]

Third, the wide age ranges of paediatric recipients pose unique challenges[10] and opportunities to expand our understanding of immune tolerance. As noted in Section 1, children transplanted in infancy have an immunologic advantage compared to older patients. Infants and young children have relatively few memory B- and T-cells.[13] Hence, their immune responses to allotransplantation are better represented as a primary immune response; hence, they may be better suited for testing for spontaneous tolerance.[32] ABO-incompatible heart transplantation during infancy results in long-term absence of antibodies specifically towards the donor blood group A and B antigens due to absence of specific B-cells [15] and modified evolution of B-cell memory in presence of an ABO-incompatible organ.[13] Surprisingly, patients after ABO-incompatible transplant show less de novo Human Leukocyte Antigen sensitisation,[33,34] fewer rejection, and bacterial infections than clinically similar recipients of compatible organs, suggesting a lasting benefit of these immune alterations that could also benefit older age groups.[35] Better methods to assess an individual's immune status in real time could lead to the management of their unique immune systems and provide many learning opportunities for the "personalisation" of intensity and scope of immunosuppression following paediatric heart transplantation. Major additional funding will be required to elucidate the immunological basis for this relative tolerance seen in immature recipients and to develop technologies for monitoring their immunologic responses to the transplanted heart.

Fourth, the evolving indications and timing for paediatric heart transplantation create unique challenges in meeting the expectations of parents and patients for long-term survival. However, these children are often referred for paediatric heart transplantation after multiple prior operations.[36] The reality of multiple blood transfusions and incorporation of antigenic reconstructive materials can frequently lead to sensitisation. While extensive studies have examined desensitisation in adult patients, the challenges of small numbers and inter-patient variability require costly multi-centre studies to make meaningful progress in minimising sensitisation and its sequelae. Staged Fontan palliation of single ventricle has been linked to hepatic scarring and cirrhosis, and these patients are increasingly being referred for heart or combined heart–liver transplantation, but the optimal timing is uncertain.[37] Costly multi-centre studies will be required to clarify the point of irreversible hepatic damage that would preclude isolated heart transplantation.

Fifth, the incremental risks associated with heart transplantation in children of different ethnicities and races are incompletely understood. Recent studies have shown a significant contribution of societal factors on disadvantages for ethnic groups regarding transplant listing access and outcomes[38] and unintentional biases in healthcare providers.[39,40] The higher risk of post-transplant mortality among Black recipients is well established,[41] identifying the relative impact(s) of immunologic differences versus socio-economic and healthcare access issues will require costly multi-centre studies to clarify and address these challenges.

In summary, the limited transplant experience at single centres requires time-consuming and costly multi-institutional studies and trials and dissuades for-profit investment for devices and drugs. The smaller number of paediatric heart transplantation recipients and the ~10-fold greater number of adult heart transplant recipients creates a "most good" advantage of the later in grant funding decisions. The Federal Drug Administration's Real-World Evidence programme provides a new path to their clearance/approval for device trials in children. The Real-World Evidence programme has demonstrated how existing healthcare systems can collect, store, and curate data that can be utilised[42] bypassing traditional randomised controlled trials, which are costly and pose challenges for complete data collection. Philanthropic organisations such as Enduring Hearts, often in collaboration with dedicated professional societies, such as the Pediatric Heart Transplant Study Group, International Society of Heart Lung Transplantation, and the American Heart Association, are providing important research funding for paediatric heart transplant recipients. However, much more funding will be needed to advance strategies to enhance their long-term survival and quality of life. Ironically, while most scientific discoveries emanating from studies in paediatric heart transplant recipients are quickly translated to adult recipients with highest "market values," the reverse pathway often requires considerable, and often

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unmet, funding to evaluate efficacy and safety in paediatric heart transplant recipients. Considering these realities, advocacy for funding and application of incentives, such as in Orphan Drug rules in the United States and upholding principles of equity and inclusion in institutional research support, are critical to ensuring scientific progress for paediatric heart transplant recipients worldwide. That paediatric heart transplantation is life-saving therapy should inspire us to advocate for funding more searches for cures.

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