Cardiology in the Young (2015), **25(Suppl. 2)**, 131–139
doi:10.1017/S1047951115000931

Original Article

More lessons learned from the Pediatric Heart Transplant Study*

Yuk M. Law[1,2]

[1]*Division of Pediatric Cardiology, Seattle Children's Hospital;* [2]*Division of Pediatric Cardiology, University of Washington, Seattle, Washington, United States of America*

Abstract Paediatric heart transplantation has evolved over the last 3 decades. The research group, Pediatric Heart Transplant Study, has been in step with that evolution over the nearly 20 years of its existence by utilising its registry to contribute a wealth of clinical research to the field. The highlights of its studies will be presented in this review.

Keywords: Heart transplantation; children; pediatrics; registry

Received: 5 February 2015; Accepted: 1 May 2015

Background

Within the field of paediatric cardiology and cardiac surgery, the natural history of heart transplantation is truly expansive in that it covers the phase before transplant, the so called waiting period, the transplant procedure itself, and the long-term follow-up that remains for many an "open book". In many ways, the anonymous stories of the individual patients who had the courage to take this journey are captured collectively in the archives of the Pediatric Heart Transplant Study.

The creation of the Pediatric Heart Transplant Study was in essence a natural consequence of the early history of paediatric heart transplantation. It is generally considered public knowledge that Christiaan Barnard performed the first human heart transplantation in an adult man in South Africa in 1967; however, it is largely medical trivia for physicians and laymen alike that only 3 days later a heart transplant was performed in an infant in New York City by Adrian Kantrowics.[1] Neither this infant with Ebstein's anomaly nor the adult in Cape Town survived for very long, but as history would have it they paved the way to the current success we see in modern heart transplantation in adults and children. Pediatric Heart Transplant Study, in my mind, is a by-product if not a landmark in the history of paediatric heart transplantation.

As paediatric heart transplantation gained momentum through the pioneering work of Sir Magdi Yacoub in Europe, Len Bailey with xenogeneic and neonatal transplantations in the United States, and Denton Cooley with the first long-term successful survivor, a growing number of American centres were performing heart transplantation in children in the 1980s.[2,3] In fact, by the early 1990s, the steep growth in transplant volume reached its first plateau (Fig 1). It was apparent that heart transplantation in children was quite different than in adults. Candidates in this early period were dominated by infants with irreparable CHD. The transplant procedure itself required re-constructive surgery in addition to anastomosing the allograft. The co-morbidities before and after transplant were recognised to be different, leading to very different medical requirements not just in the amount and how immunosuppressive medications were to be delivered. These differences led to the recognition that the management of children cannot be simply based on adult data. These differences in care between adults and children plus the development of a critical mass of practitioners and patients led to the need to form a heart transplant registry specific for children – the Pediatric Heart Transplant Study. The foresight of the Pediatric Heart Transplant Study "founders" allowed this registry to flourish into a vast database with a prolific output of clinical research studies published that will be reviewed below.

*Presented at Johns Hopkins All Children's Heart Institute, International Pediatric Heart Failure Summit, Saint Petersburg, Florida, United States of America, 4–5 February, 2015.

Correspondence to: Y. M. Law, Division of Pediatric Cardiology, Seattle Children's Hospital and University of Washington, 4800 Sand Point Way NE, Seattle, WA 98105, United States of America. Tel: +206 987 4233; Fax: +206 987 3839; E-mail: yuk.law@seattlechildrens.org

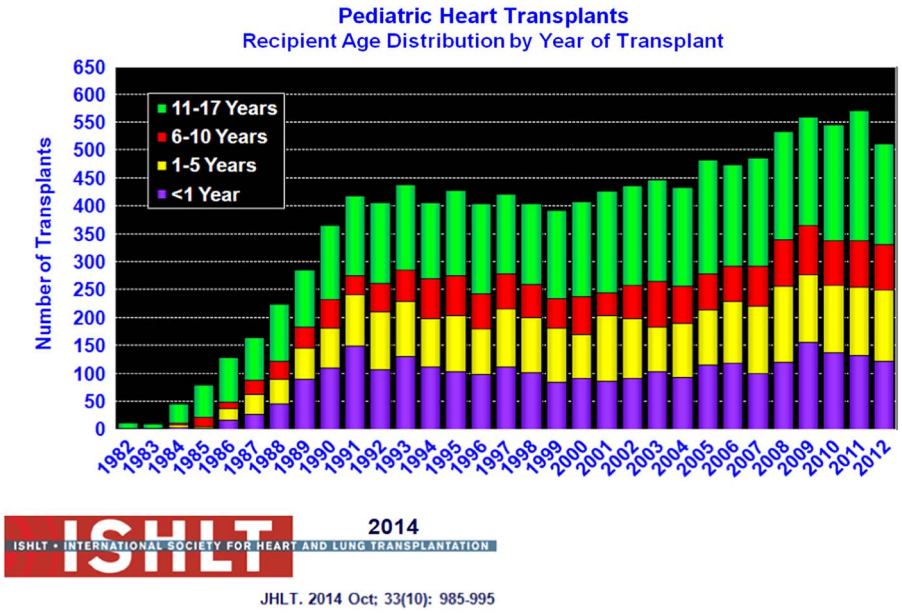

Figure 1.
Number of transplants by age and year.

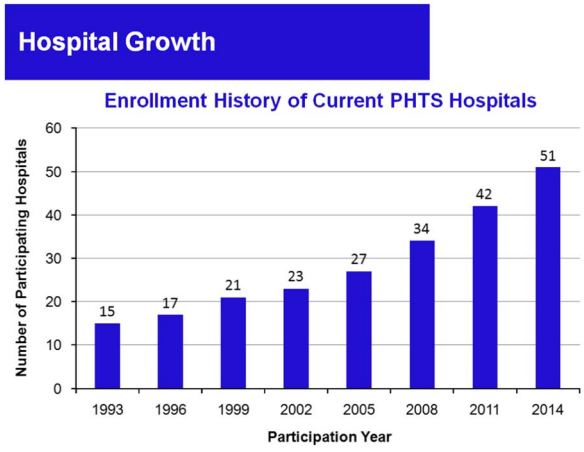

Figure 2.
Growth of the PHTS membership. PHTS = Pediatric Heart Transplant Study.

Figure 3.
Map of participating centres in PHTS. PHTS = Pediatric Heart Transplant Study.

The newly formed study group started with 15 centres, and data collection began in 1993. It has grown to 51 centres in 2014, covering three continents and four countries (Fig 2). The majority of centres are from the United States, but the newer members are likely from South America, Pacific Rim, and Europe (Fig 3).

The operation and productivity of the Pediatric Heart Transplant Study

The Pediatric Heart Transplant Study database is housed and managed at the University of Alabama, Birmingham, under David Naftel and James Kirklin with the help of a biostatistical and administrative team. A database committee selected from the membership updates the database, including periodic revisions of the data collected from individual centres. A scientific committee reviews annual scientific proposals and guides the accepted studies to final publication. The steering committee, chaired by the elected president and vice president to the Pediatric Heart Transplant Study, oversees the entire operation of the organisation. A more recently

https://doi.org/10.1017/S1047951115000931 Published online by Cambridge University Press

created Foundation assists with acquiring philanthropic support. Member centres provide the clinical information about patients at time of listing, transplant, annually, and when major events occur. These events include rejection, coronary evaluation, coronary intervention, serious infections, malignancies, dialysis, mechanical circulatory support, re-transplantation, and death. As of January, 2015, there are 6629 listings and 5050 transplants registered. Since 1993, there have been 54 original scientific studies, one book chapter, one monograph, and three reviews published from the Pediatric Heart Transplant Study. There are three more publications in press and seven more to be submitted in 2015. Pediatric Heart Transplant Study also collaborates with other study grants and registries such as the Specialized Centers for Clinically Oriented Research, International Society for Heart and Lung Transplant Registry, Pediatric Cardiomyopathy Registry, and the Cardiac Transplant Registry Database (adult patients).

Figure 4 illustrates the number of publications by year. Pediatric Heart Transplant Study studies are frequently cited by cardiovascular journals – for example, in a query in the Web of Science, the median frequency of Pediatric Heart Transplant Study publications being cited is 15 (interquartile range 6–52).

The following are the lessons learned in the field of paediatric heart transplantation from investigative studies published by Pediatric Heart Transplant Study; two other substantial reviews complement the data reviewed below.[4,5]

Research methodology

Although not original research, Naftel and his statistical group at the Pediatric Heart Transplant Study put forth the applicability of competing risk analysis in transplantation outcome research.[6] The time to an event is a common measure of probability over time, and the method of Kaplan and Meier is commonly used to depict this; however, in transplantation and other cardiovascular conditions, multiple, exclusive outcomes compete with each other and should be taken into consideration in estimating the probability of an outcome of interest – for example, the probability of transplantation after listing – wait list duration – is affected by the probability of death, removal from listing because of improvement, removal because of ineligibility, and remaining on the list. The time-dependent occurrence of an event – transplant, death, complications, allograft loss, and remaining on list – and its different competing outcomes are highly pertinent to transplant outcome research, and the work of the Pediatric Heart

Figure 4.
Number of PHTS studies published since its inception. PHTS = Pediatric Heart Transplant Study.

https://doi.org/10.1017/S1047951115000931 Published online by Cambridge University Press

Transplant Study group has certainly advanced our understanding of how best to approach this analysis.

Risk factors for transplant outcome

Clearly, it is of high clinical impact to identify risk factors for poor outcome after transplantation. Thus, the inaugural Pediatric Heart Transplant Study studies examined this issue.[7] These risk factors included young age, need for mechanical circulatory assistance that equated to extracorporeal membrane oxygenation in this era, and non-identical ABO blood type. In this early era, many of the transplant recipients were infants, in whom complex CHD and hypoplastic left heart syndrome were common diagnoses. A separate analysis of recipients <1 year of age by Canter et al[8] showed that non-identical ABO blood type and previous surgery were risk factors. Interestingly, for the infant group, allograft ischaemic time, need for ventilator or inotropic support, and waiting time were not associated with a poor transplant outcome. These studies also depicted overall early to short-term survival and were comparable with contemporary adult outcomes. Although the composition of the candidates listed for transplant has changed over time, shifting away from primary listing for hypoplastic left heart syndrome in the infant population, many of these risk factors have remained important in the risk assessment of the transplant candidate.

Other potential risk factors were substantiated by the large cohort size, possible with the Pediatric Heart Transplant Study registry. These included the consistent findings that CHD was a greater risk factor when compared with cardiomyopathies. This is particularly seen in young adults with CHD at one extreme versus children with cardiomyopathy at the other extreme of best outcome.[9] Another group of patients with CHD that emerged requiring transplant over time and having its unique cardiovascular complications was the Fontan patients group. The Pediatric Heart Transplant Study multi-centre study was the first that rigorously evaluated the outcome of this group from listing to post-transplant.[10] Overall wait list survival was not different from patients with CHD or cardiomyopathy. Upon further inspection, young age, ventilator support, status 1, and short time since Fontan palliation were risk factors for death while waiting. This underscored the importance of properly selecting candidates for the Fontan procedure, as acute low cardiac output failure after the Fontan is difficult to manage. Post-transplant survival was not as good as in patients with CHD (not statistically significant) or cardiomyopathy (statistically significant). This was also the first study to demonstrate that, as a group, protein-losing enteropathy resolved in all those who survived transplant past 30 days (n = 19).

The problem of human leucocyte antigen sensitisation was also studied. Not only did sensitisation increase wait list time in centres waiting for a potential negative crossmatch but also in those recipients who went on to receive an organ with a positive crossmatch (candidate's serum reacts against the donor lymphocytes), and there was an increase in mortality.[11] Sensitisation is a highly vexing problem, because in the repair of CHD exposure to blood products and the use of homograft are common, further complicating the high-risk nature of transplantation in patients with CHDs.

Infants with CHD

There has been focussed attention on this subpopulation. In ways, the impetus to the development of paediatric heart transplantation revolved around CHDs that do not have a good outcome from surgical repair, such as hypoplastic left heart syndrome in the 1980s–1990s. Kichuk-Chrisant et al[12] looked back at this era where primary transplant listing of hypoplastic left heart syndrome was not uncommon. Young infants with this condition have one of the highest waiting times among children, a high wait list mortality (25%), and also higher post-transplant mortality. The other problem identified is that those who switched from waiting for transplant to Norwood, probably because the wait was inexorable, did not do well after their palliation. Of this small group of 23 patients, 52% died after repair. This high mortality is likely due to undertaking a delayed Norwood procedure (average of 43 days), which is itself a risk factor in patients not listed for transplant. Despite these adversities, long-term survival caught up with other sub-populations and this was a common theme observed by the transplant community: regardless of their high-risk status, going into transplant, young children do very well if they survive past the early post-transplant period.

Everitt et al[13] studied infants requiring transplant after the Norwood procedure but before the Glenn procedure in a more contemporary cohort (1993–2008). This is a more typical scenario in the modern era of patients with hypoplastic left heart syndrome requiring transplant. Unfortunately, these patients did the worst after transplantion (70% at 1 year) compared with same-age groups with cardiomyopathy, hypoplastic left heart syndrome without Norwood, and other CHDs with or without surgery.

Gulersarian et al[14] turned the focus on infants with single ventricle circulation without hypoplastic left heart syndrome who required transplantation. Many of these patients had the most complex anatomy that

https://doi.org/10.1017/S1047951115000931 Published online by Cambridge University Press

presumably were deemed "irreparable" in a definitive way, as opposed to simply unsatisfactory repair results leading to the choice of primary listing for transplantation. Interestingly, the outcome of these infants during the waiting period could be stratified by whether they had some form of surgical palliation, and it was those who were not palliated who did the worst. As explained by the authors, it is likely that there is no good medical or interventional palliation that can keep such non-operated infants stable while waiting, if, for example, they have an unstable coronary circulation, such as in pulmonary atresia with intact septum and coronary insufficiency, atrioventricular valve regurgitation, etc. Durable mechanical circulatory support is typically not feasible in the single ventricle circulation.

A cumulative lesson learned from infants with CHD is that one must look at the overall outcome from either birth or listing to long-term follow-up after transplantation. Although transplant recipients do fare quite well in the long term, ultimately, it is this overall outcome that is meaningful to the patient. With the Norwood procedure having much better success and the availability of infant donors limited, it is rare in the current era that a newborn with standard risk would undergo primary listing for heart transplantation.

Wait list mortality

The other significant at-risk period is that during the waiting period. Here, the infants with blood group O are again disadvantaged as shown in a study by Morrow et al[15] Although the majority of the population is composed of blood group O, other blood groups can accept an O donor, thereby competing with the O candidates. Kirklin et al[16] examined the use of organs for more stable candidates (status 2) and whether organs preferentially going to these recipients because they are geographically more proximal to the origin of the donor has clinical merit. The results of this study illustrated the difficulty in only transplanting the sickest of the sick, because these highly sick patients are also at higher risk of death after transplant, whereas the more stable patients do very well as expected. The other concern is that many status 2 candidates deteriorate to status 1 and may miss the window of an uneventful transplant course.

There have also been studies carried out on the primary cardiomyopathy population, some of which in collaboration with the Pediatric Cardiomyopathy registry. Singh et al[17] showed that the severity of left ventricular enlargement in dilated cardiomyopathy is associated with combined mortality during the waiting and early post-transplant periods, particularly among younger patients. As previously observed, however, cardiomyopathy recipients do have better survival than patients with CHD, and within the cardiomyopathy group patients with the dilated phenotype do better than restrictive or hypertrophic phenotypes, also particularly so in younger children.[18] In general, patients presenting with heart failure requiring intense support early in life with hypertrophic cardiomyopathy[19] or restrictive cardiomyopathy[20] do not do as well as patients with dilated cardiomyopathy. There is also a "signal" from the registry data that patients with cardiomyopathy from myocarditis have a poorer early survival due to increased rejection.[21]

Mechanical circulatory support

With the advent of durable ventricular assist devices, Pediatric Heart Transplant Study reviewed registrants bridged to transplant with this mode of support. It was the first large-scale study of assist devices in children, and provided promising results in that 86% of the supported patients went on to receive a transplant.[22] The cohort was older and larger in this first-generation device study. Younger patients and those with CHD were the higher-risk groups. Nevertheless, the overall cohort had similar post-transplant survival compared with priority 1A-listed recipients who were not supported with a ventricular assist device.

Transplant rejection

As Pediatric Heart Transplant Study matured and longitudinal data accrued, the group began to focus on post-transplant management. The mainstay of solid organ transplant immunosuppression consists of a calcineurin inhibitor – tacrolimus or cyclosporine – and an adjunctive anti-metabolite agent plus a period of steroids. The exact timing of initiation and dosing is quite variable among centres, but the outcome measure of rejection versus over immunosuppression represented by malignancy/infection can at least be evaluated in a large-scale manner using registry data. It also became apparent that in addition to grading rejection by the severity of histological inflammation and cellular necrosis, rejection can be further classified in a clinical way such as early – within 12 months from transplant – late onset – beyond 12 months and typically a period of quiescence before unexpected rejection occurs – recurrent, and haemodynamically compromised, which means when signs and symptoms of heart failure or gross graft dysfunction are apparent. These various ways of characterising how rejection presents may have prognostic implications – for example, Pahl et al[23] followed by a revisit by Everitt et al[24] demonstrated an association of

https://doi.org/10.1017/S1047951115000931 Published online by Cambridge University Press

haemodynamically compromised rejection (in 25% of Pediatric Heart Transplant Study population) with poor outcome. Importantly, in these inter-era studies, the frequency of severe haemodynamically compromised rejection, 9%, has not changed. Webber et al[25] showed that late rejection was not uncommon (27% at 3 years), and when it is of the haemodynamically compromised type it is also associated with mortality. There was also a follow-up study on late rejection by Ameduri et al[26], and it showed this form of rejection to be less common in the current era, but continued to be associated with mortality and the development of cardiac allograft vasculopathy. The risk factors were black race, male donor, older age, and era. Early rejection has also seen a decline over the years, decreasing from 60 to 40% in the 1st year in the more recent era.[27] Recurrent rejection has also been further characterised by Pediatric Heart Transplant Study. Recurrent rejection was more common in the early post-transplant period and after initial rejection treatment, which raises the concern of inadequate rescue treatment for rejection.[28]

Pediatric Heart Transplant Study is quite apt at depicting events and outcomes while identifying their associated risk factors; however, being a registry that collects data relatively infrequently after transplant, it is not prepared to assess the effects of medical therapy. In all the Pediatric Heart Transplant Study studies published, there are only two that make an attempt at investigating medical intervention. Boucek et al[29] performed a centre-directed, non-randomised, single-arm, prospective study of the anti-lymphocyte globulin administered early after transplantation to prevent rejection. This intervention is called induction immunotherapy in the field of transplantation and is meant to prevent future rejection, whereasin a more pragmatic way provides clinicians time to up-titrate oral immunosuppressive drugs. There was an improvement in survival in the treatment arm but no significant difference in rejection frequency. As the treatment arm resided with centres that used anti-lymphocyte globulin, when the analysis was carried out with the intention to treat, which included patients who were excluded from receiving induction in these same centres, the survival advantage was no longer observed. Although the efficacy of induction can be debated, there was no safety concern in follow-up in those who received rabbit anti-thymocyte globulin as opposed to OKT3. Since that time, more centres are using rabbit anti-thymocyte globulin as the induction therapy of choice. Gajarski et al[30] reported that 71% of the centres now use induction consisting of various kinds of antibodies and that there continues to be no association with malignancies or opportunistic infections.

Transplant complications: infections, malignancies, cardiac allograft vasculopathy, and renal dysfunction

Infection is the Achilles heel of immunosuppression. In the modern armamentarium of immunosuppression, it is theoretically possible to eliminate rejection in the standard patient, but the experience of the transplant physician will suggest that serious infections replace rejection events. In young children, many may not have been fully immunised before their transplant, and after transplant vaccinations may not be as effective. Viral pathogens such as cytomegalovirus and Epstein-Barr virus transmitted through blood products can infect immunologically naïve patients in a most inopportune manner, such as early after transplant when the immune system is most suppressed. Furthermore, chronically ill, hospitalised, malnourished patients with surgical drains, indwelling catheters, endotracheal tubes, and wounds are at serious risk for infections. Schowengerdt et al[31] showed that infections are more common in the 1st year after transplantation and infants suffer more serious consequences. Bacterial infections reach their peak in the 1st month, cytomegalovirus infections in the 2nd month, and fungal infections are associated with high mortality. George et al[32] also demonstrated that the risk of death from infection is inversely related to the risk of death from rejection when it is modelled with respect to age – for example, adolescents are much more at risk of death from rejection than they are for death from infection, whereas elderly recipients are at higher risk for death from infection than from rejection (Fig 5).

A scourge of paediatric transplantation related to infection is post-transplant lymphoproliferative disease. Malignancies in general are highly unusual in the paediatric population except for this virus-driven infection that transforms an infection into a lymphoma-type malignancy. Of the same family as the cytomegalovirus, the Epstein-Barr virus is transmitted from humans and can be acquired from the donor organ, blood transfusions, or through natural human contact over time. As most young recipients are naïve to this virus and there is no Epstein-Barr virus vaccine, an inopportune infection when the immune system is highly suppressed patients the recipient to the risk of a serious infection by this virus that cannot be controlled by the host's immune system under immunosuppression. Webber et al[33] showed the cumulative incidence of post-transplant lymphoproliferative disease to be 8% at 5 years. The survival after diagnosis was 68% at 3 years, and death from the disease was similar to death from graft loss due to complications related to

https://doi.org/10.1017/S1047951115000931 Published online by Cambridge University Press

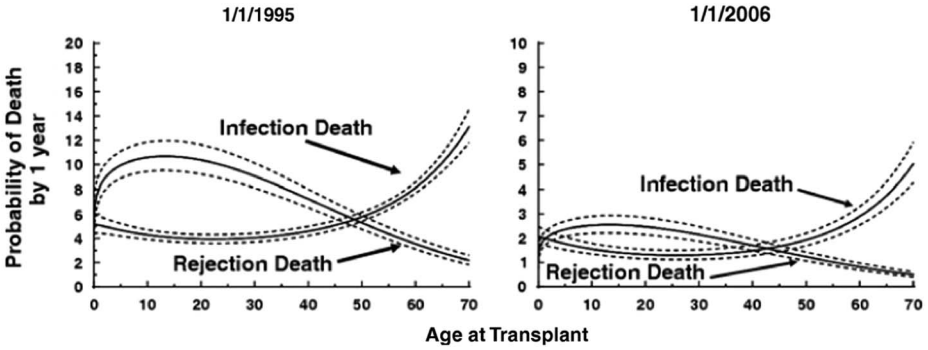

Figure 5.
Probability of death from infection and rejection as a function of age in an earlier and later era.[31]

rejection as the treatment entails the withholding of immunosuppression with or without chemotherapy. Intense chemotherapy itself is also not well-tolerated by the transplant recipient and these patients with significant past medical and surgical histories can succumb to the adverse effects of chemotherapy.

The other as yet insurmountable and literally inherent complication of heart transplantation is cardiac allograft vasculopathy or coronary disease of the transplant heart. The interface between the immune system of the host and the allograft is in the coronary vasculature; therefore, perhaps it is no wonder that even without a history of diagnosable rejections, allograft vasculopathy can still develop. Pahl et al[34] estimates the development of the complication to be 17% at 5 years, which appears to be less common than in adult recipients. Risk factors include age of donor, age of recipient at transplant, and greater than one rejection episode in the 1st year. There is definitely an association with the loss of the allograft. An updated study is in progress from Pediatric Heart Transplant Study.

Renal disease often co-exists with heart disease, particularly in those who are haemodynamically compromised or experience severe acute or chronic heart failure. Some degree of pre-transplant dysfunction can certainly persist after transplantation; however, calcineurin inhibitors are required lifelong in the transplant recipient and they have direct renal toxic effects. Feingold et al[35] examined late renal function after transplant. Although only 1.4% of the Pediatric Heart Transplant Study cohort required dialysis or renal transplant, renal dysfunction was common in the long-term follow-up with only 57% of the recipients free from renal dysfunction (estimated glomerular filtration rate >60 ml/minute/1.73 m^2) at 10 years after transplant. Haemodynamically compromised rejection in the 1st year, black race, and renal function at 12 months were independent risk factors.

Conclusions

The Pediatric Heart Transplant Study has provided a wealth of investigative and clinical information to the field of paediatric heart transplantation. The work of the registry has made a tremendous impact on clinical practice. This is particularly true of depicting outcomes before and after transplantation and of risk assessment. These large-scale studies with the use of advanced statistics have served as the benchmark for policy-making and institutional programme development.

Another consequence of the Pediatric Heart Transplant Study is the community it has created. The paediatric heart transplant community is not large enough to form its own society. Through the membership of the Pediatric Heart Transplant Study, annual meetings, rotation of service on committees, and involvement of many individuals to work on multiple writing groups to finish a proposed study, Pediatric Heart Transplant Study has become the de facto, unofficial paediatric heart transplant society. With an existence now approaching 20 years, many clinicians and academicians alike have been trained and advanced in their career through their involvement with Pediatric Heart Transplant Study.

There remain challenges to the registry and as a consequence to the paediatric heart transplant community. Most of the major, must ask clinical and research questions have been addressed. New, emerging ones are not always amenable to be studied if the data collected are not revised. Although more centres will likely enroll, an expansion or major revision of the data collection forms can stress the already tenuous conditions at many centres that are cutting back support for ancillary staff that is not bringing in their own funding. Finally, as the metrics for outcome and risk assessment have been described, practitioners are eager to better understand medical treatment and its effects – for example, although a scientific statement exists in the field of paediatric heart transplantation,

it pertains to the indications for transplantation. A consensus guideline for the management of paediatric transplant patients with high levels of evidence to back strong recommendations is lacking. Pediatric Heart Transplant Study, akin to other registries, is not designed to study medical intervention. Clinical trials are sorely needed for paediatric cardiac diseases and heart transplantation is no exception. It will take additional leadership, collaboration, and determination by the members collectively to launch prospective studies. Given the track record of the Pediatric Heart Transplant Study, the field should be in a good place for this new endeavor to take root.

Acknowledgement

The author extends his appreciation to Susanna Lenderman from Pediatric Heart Transplant Study for her provision of Pediatric Heart Transplant Study data for this manuscript.

Financial Support

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Conflicts of Interest

None.

References

1. Kantrowics A. America's first human heart transplantation: the concept, the planning, and the furor. ASAIO J 1998; 44: 244–252.
2. Mendelhoff EN. The history of pediatric heart and lung transplantation. Pediatr Transplant 2002; 6: 270–279.
3. Chinnock RE, Bailey LL. Heart transplantation for congenital heart disease in the first year. Curr Cardiol Rev 2011; 7: 72–84.
4. Hsu D, Naftel D, Webber S, et al. Lessons learned from the pediatric heart transplant study. Congenit Heart Dis 2006; 1: 54–62.
5. Dipchand A, Kirk R, Mahle W, et al. Ten years of pediatric heart transplantation: a report from the pediatric heart transplant study. Pediatr Transplant 2013; 17: 99–111.
6. McGiffin D, Naftel D, Kirklin J, et al. Predicting outcome after listing for heart transplantation in children: comparison of Kaplan-Meier and parametric competing risk analysis. J Heart Lung Transplant 1997; 16: 713–722.
7. Shaddy R, Naftel D, Boyle G, et al. Outcome of cardiac transplantation in children: survival in a contemporary multi-institutional experience and the pediatric heart transplant study. Circulation 1996; 94 (Suppl II): 69–73.
8. Canter C, Naftel D, Caldwell R, et al. Survival and risk factors for death after cardiac transplantation in infants: a multi-institutional study. Circulation 1997; 96: 227–231.
9. Lamour J, Kanter K, Naftel D, et al. The effect of age, diagnosis, and previous surgery in children and adults undergoing heart transplantation for congenital heart disease. J Am Coll Cardiol 2009; 7: 160–165.
10. Bernstein D, Naftel D, Chin C, et al. Outcome of listing for cardiac transplantation for failed Fontan: a multi-institutional study. Circulation 2006; 25: 273–280.
11. Mahle W, Tresler M, Edens E, et al. Allosensitization and outcomes in pediatric heart transplantation. J Heart Lung Transplant 2011; 30: 1221–1227.
12. Chrisant MRK, Naftel DC, Drummond-Webb J, et al. Fate of infants with hypoplastic left heart syndrome listed for cardiac transplantation: a multi-center study. J Heart Lung Transplant 2005; 24: 576–582.
13. Everitt M, Boyle G, Schechtman K, et al. Early survival after heart transplant in young infants is lowest after failed single-ventricle palliation: a multi-institutional study. J Heart Lung Transplant 2012; 31: 509–516.
14. Guleserian K, Schechtman K, Zheng J, et al. Outcomes following listing for primary transplantation for infants with unoperated Non-Hypoplastic Left Heart Syndrome (Non-HLHS) congenital heart disease: a multi-institutional study. J Heart Lung Transplant 2011; 30: 1023–1032.
15. Morrow R, Naftel D, Chinnock R, et al. Outcome of listing for heart transplantation in infants younger than six months: predictors of death and interval to transplantation. J Heart Lung Transplant 1997; 16: 1255–1266.
16. Kirklin J, Naftel D, Pearce F, et al. Should status II patients be removed from the pediatric heart transplant waiting list? A multi-institutional study. J Heart Lung Transplant 2006; 25: 271–275.
17. Singh T, Sleeper L, Lipshultz S, et al. Association of left ventricular dilation at listing for heart transplant with post-listing and early post-transplant mortality in children with dilated cardiomyopathy. Circulation 2009; 28: 591–598.
18. Dipchand A, Naftel D, Feingold B, et al. Outcomes of children with cardiomyopathy listed for transplant: a multi-institutional study. J Heart Lung Transplant 2009; 28: 1312–1321.
19. Gajarski R, Naftel D, Pahl E, et al. Outcomes of pediatric patients with hypertrophic cardiomyopathy listed for transplant. J Heart Lung Transplant 2009; 28: 1329–1334.
20. Zangwill S, Naftel S, L'Ecuyer T, et al. Outcomes of children with restrictive cardiomyopathy listed for heart transplant: a multi-institutional study. J Heart Lung Transplant 2009; 28: 1335–1340.
21. Pietra B, Kantor P, Bartlett H, et al. Early predictors of survival to and after heart transplantation in children with dilated cardiomyopathy. Circulation 2012; 126: 1079–1086.
22. Blume E, Naftel D, Bastardi H, Duncan B, Kirklin J, Webber S. Outcomes of children bridged to heart transplantation with ventricular assist devices: a multi-institutional study. Circulation 2006; 113: 2313–2319.
23. Pahl E, Naftel D, Canter C, Frazier E, Kirklin J, Morrow W. Death after rejection with severe hemodynamic compromise in pediatric heart transplant recipients: a multi-institutional study. J Heart Lung Transplant 2001; 20: 279–287.
24. Everitt M, Pahl E, Schechtman K. Rejection with hemodynamic compromise in the current era of pediatric heart transplantation: a multi-institutional study. J Heart Lung Transplant 2010; 30: 282–288.
25. Webber S, Naftel D, Parker J. Late rejection episodes more than 1 year after pediatric heart transplantation: risk factors and outcomes. J Heart Lung Transplant 2003; 22: 869–875.
26. Ameduri R, Zheng J, Schechtman K. Has late rejection decreased in pediatric heart transplantation in the current era? A multi-institutional study. J Heart Lung Transplant 2012; 31: 980–986.
27. Gossett J, Canter C, Zheng J, et al. Decline in rejection in the first year after pediatric cardiac transplantation: a multi-institutional study. J Heart Lung Transplant 2010; 29: 625–632.
28. Chin C, Naftel D, Singh T, et al. Risk factors for recurrent rejection in pediatric heart transplantation: a multicenter experience. J Heart Lung Transplant 2004; 23: 178–185.

29. Boucek R, Naftel D, Boucek M, et al. Induction immunotherapy in pediatric heart transplant recipients: a multi-center evaluation. J Heart Lung Transplant 1999; 18: 460–469.
30. Gajarski R, Blume E, Urshel S, et al. Infection and malignancy after pediatric heart transplantation: the role of induction therapy. J Heart Lung Transplant 2011; 30: 299–308.
31. Schowengerdt K, Naftel D, Seib P, et al. Infection after pediatric heart transplantation: results of a multi-institutional study. J Heart Lung Transplant 1997; 16: 1207–1216.
32. George J, Taylor D, Blume E, et al. Minimizing infection and rejection death: clues acquired from 19 years of multi-institutional cardiac transplantation data. J Heart Lung Transplant 2011; 30: 151–157.
33. Webber S, Naftel D, Fricker F, et al. Lymphoproliferative disorders after paediatric heart transplantation: a multi-institutional study. Lancet 2006; 367: 233–239.
34. Pahl E, Naftel D, Kuhn M, et al. The impact and outcome of transplant coronary artery disease in a pediatric population: a 9 year multi-institutional. J Heart Lung Transplant 2005; 24: 645–651.
35. Feingold B, Zheng J, Law Y, et al. Risk factors for late renal dysfunction after pediatric heart transplantation: a multi-institutional study. Pediatr Transplant 2011; 15: 699–705.