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Part III: Review of the Impact of Donor Characteristics on Pediatric Heart Transplant Outcomes

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Abbreviations:

HTx: heart transplantation

HIV: Human immunodeficiency virus

ISHLT: International Society of Heart and Lung Transplantation

DRWR: donor recipient weight ratio

PVR: pulmonary vascular resistance

OPTN: Organ Procurement and Transplantation Network

DCM: Dilated cardiomyopathy

DRHR: donor recipient height ratio
UNOS: United Network for Organ Sharing
CT: computerized tomography
MRI: Magnetic resonance imaging
CAV: cardiac allograft vasculopathy
ABO-I: ABO incompatible
PTLD: Post-transplant lymphoproliferative disorder
HLA: human leukocyte antigen
AMR: antibody mediated rejection
SRTR: Scientific Registry of Transplant Recipients
HBV: Hepatitis B virus
HCV: Hepatitis C virus
NAT: Nucleic acid test
HBsAB: Hepatitis B surface antibody
HBsAg: Hepatitis B surface antigen
HBcAB: Hepatitis C antibody
HBIG: Hepatitis B immunoglobulin
HTLV-1: Human T-Lymphotropic Virus Type 1
D: Donor
R: Recipient
MDR: multi-drug resistant
TB: Mycobacterium tuberculosis

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ABSTRACT

Background:

Heart transplantation (HTx) is a treatment option for end-stage heart failure in children. HTx is limited by the availability and acceptability of donor hearts. Refusal of donor hearts has been reported to be common with reasons for refusal including pre-existing donor characteristics. This review will focus on the impact of donor characteristics and comorbidities on outcomes following pediatric HTx.

Methods:

A literature review was performed to identify articles on donor characteristics and comorbidities and pediatric HTx outcomes.

Results:

There are many factors to consider when accepting a donor heart. Weight based matching is the most common form of matching in pediatric HTx with a donor recipient weight ratio between 0.7 and 3 having limited impact on outcomes. From an age perspective, donors <50 years, can be carefully considered but the impact of ischemic time needs to be understood. To increase the donor pool, with minimal impact on outcomes, ABO-incompatible donors should be considered in patients that are eligible. Other factors to be considered when accepting an organ include donor comorbidities. Little is known about this in the pediatric population, with most of the data focusing on infections. Being aware of the potential infections in the donor, understand testing available and risks of transmission, as well as treatment options for the recipient is essential.

Conclusions:

There are a number of donor characteristics that potentially impact outcomes following pediatric HTx but these need to be taken into along with their interactions with recipient factors when interpreting the outcomes following HTx.

INTRODUCTION

Heart transplantation remains an important treatment strategy for end-stage heart failure in children. Unlike mechanical therapies, transplantation is limited by both the availability and acceptability of donor hearts. Refusal of donor hearts in pediatrics has been reported to be common ^{1,2}. Reasons for refusal vary with pre-existing donor characteristics potentially playing a role. The impact of donor characteristics, many of which are non-modifiable, on both short and long-term outcomes has been the focus of a number of studies. However, the understanding of the impact of donor characteristics and comorbidities on pediatric heart transplant remains limited due to multiple factors including small cohorts, lack of randomized control trials, and the global challenges of studying donor characteristics. Due to these issues the majority of data available for review is predominantly single center retrospective cohort studies intermingling with retrospective database analyses and case reports. In this section we will explore the impact of donor demographics, co-morbidities and infections on outcomes post-transplant, recognizing that outcomes cannot be solely attributed to these factors but must take into account recipient and donor-recipient interactions.

METHODS

A literature search was performed in Medline database in October 2018, including the MESH Headings: 'Tissue Donor', 'Heart Transplantation', 'Heart', 'Transplant', 'infant', 'child', 'adolescent' along with the following terms: donor, Cardiac, graft, Child or variation of child. The search was limited to the English Language, humans and year greater than 2010. After removing duplicates 500 articles remained (n=500). These articles were screened by two authors for relevance to the subjects within the review (n=95). These articles were then further reviewed by each of the section authors before incorporating them into

the written review. In addition, a second review was performed in Medline, EMBASE, PubMed and Cochrane Database in October 2018 that focused on infection issues, the same search terms as above but not limited to children. In addition, these terms were combined with Hepatitis, HIV, Toxoplasmosis, Parasitic Disease, Tuberculosis, Bacterial infections, encephalitis, anti-bacterial agents and variations of the term infection. This resulted in 1987 articles with 446 removed due to duplications, leaving 1541, which were screened for relevance.

DONOR DEMOGRAPHICS

Size matching

Donor selection for heart transplant recipients is a process involving complex matching of both donor and recipient characteristics. Of these characteristics, determining the appropriate size donor heart depends on a complex web of interactions that needs to be analyzed rapidly at the time of an offer.

The International Society of Heart and Lung Transplantation (ISHLT) guideline for care of the heart transplant recipient suggests a donor recipient weight ratio (DRWR) between 0.7 and 2.0, for those that are sex matched or male to female. In the case of female to male heart transplantation the DRWR suggestion was increased to 0.8 and 2.0.³ These guidelines may not necessarily apply to children given the wide range of patients and complexities that are encountered in pediatrics.

Finding the optimal size match is essential to maximize the chances of finding a suitable organ whilst limiting exposures to serious complications while waiting for transplant. The failure to accept a donor organ with a DRWR greater than 2.0, for instance, may lead to a child waiting longer, experiencing complications and in turn resulting in a worse overall outcome. For this reason, many pediatric centers around the world have modified the criteria for DRWR to include ratios outside the above ISHLT guidelines.

Several studies in children have addressed outcomes in relation to DRWR. Extending the DRWR upwards to 3.0 has been reported to be safe. Kanani et al. divided the

DRWR into three tertiles, comparing a number of different factors between tertiles⁴. An increased DRWR did not significantly increase the incidence of right heart failure, length of intubation or length of stay. Within this study there were 9 children with a DRWR >3. There was no difference between these patients and the rest of the group with respect to mortality, hypertension, right heart failure or time to discharge following transplant. These results suggest that stretching the DRWR upwards can be associated with acceptable results. Similar results have also been reported supporting a DRWR upper value of 2.0⁴.

A review of the UNOS database of 3048 pediatric recipients examined the lower end of the DRWR range and reported no difference in outcomes with a DRWR above 0.6 compared to recipients with a DRWR of ≥ 0.8 . Thirty-day mortality was significantly increased when the DRWR fell below 0.6, which is helpful when considering the lower threshold for acceptance⁵. Despite these size mismatches it is reassuring that growth and remodeling of the transplanted heart does occur over time with respect to the cardiac dimensions and myocardial mass⁶. Undersizing of donors has also been raised as a potential concern in adults. Taghavi et al. in a single center study, report the safety of using a DRWR down to 0.7 in adults⁷. There was no difference in outcome for patients following female into male transplants but they did note that the expected resolution of raised PVR after transplant was not seen when undersized donor hearts were utilized. A similar study, from 21,928 adult patients in the UNOS database, divided patients into an acceptable DRWR (>0.9), a low ratio (0.6 to 0.9) and a very low group (<0.6)⁸. The authors identified no difference in outcome when low ratio transplants were used for sex matched or male to female transplant procedures. However, for female to male transplants, an increased mortality was observed in the low ratio group. This data suggests that extending the DRWR to 0.7 is safe, as also shown in the pediatric data, and under circumstances where transplant may need to be expedited, extending to a DRWR of 0.6 in pediatric patients might be considered.

The concern with using undersized donors in pediatric patients with elevated PVR, has been examined by Zafar et al using the UNOS database⁹. They identified children with a PVR greater than 3.0 wU.m² and divided them into three groups of DRWR; <0.8 , 0.8 to 1.2 and >1.2 . There was no difference in survival between these

three groups. On sub-analysis, those recipients with DCM who had an oversized donor had better outcomes than congenital heart disease patients with an oversized donors. Therefore, the practice of placing a larger heart into a patient with raised PVR, in the context of congenital heart disease needs careful reconsideration and further research to understand these findings.

It is also important to consider whether using other size related demographic data, besides weight, to match donors and recipients is superior. Height, body mass index and body surface area all have different mathematical regression curves predicting, “heart size”. Patel et al. queried the OPTN database and included 2234 children who received transplants for DCM ¹⁰. Children identified within the cohort were divided into three groups of donor-recipient height ratio (DRHR (<0.87, 0.87 to 1.18, >1.18). The results identified an increased mortality at a year for the lowest group of DRHR. However, this effect disappeared when controlling for other confounding factors. Supported by these results and others, it does not appear that selecting suitable donor organs based on height rather than weight offers any further advantage ^{10,11}. As well as directly measurable morphometric parameters, researchers have also been interested in predicting the cardiac size of the normal “donor” population by using algorithms based on cross-sectional imaging such as CT or MRI. Studies have suggested that measuring the predicted heart mass may better predict primary graft dysfunction but not necessarily mortality ^{12–14}. No pediatric literature is available on this topic but warrants further investigation.

Other researchers have used advances in 3D reconstructions, using virtual implantation of cardiac “avatars” based on a library of expected sizes for a donor’s height and weight. Whilst this demonstrates some promise, the development remains researched based and needs further refinement prior to inclusion into recommended practice ^{15,16}.

In summary, recent evidence suggests that matching by DRWR is a robust method of identifying suitable donors. The DRWR advocated by the current ISHLT guidelines are conservative and extension of the DRWR significantly above and a little below is reasonable based on appropriate risk-benefit analysis for individual recipients. Newer methods of matching based on predictive heart mass show promise, particularly for

those recipients requiring robust cardiac output in the immediate post-transplant period.

Donor Age

The ISHLT guidelines for heart transplant care states that donors under the age of 45 years are likely to have the metabolic reserve to withstand the rigors of cold transportation even with prolonged ischemic time ³. In pediatric heart transplantation, the majority of donors are ≤ 18 years of age as outlined in the ISHLT registry. Of the 7730 pediatric transplants in the ISHLT registry report 24% (n=1841) were from donors older than 18 with 9% (n=701) being older than 31 years. However, there is a significant difference in the age range of donor hearts between Europe and North America. Less than 1% of donors used for pediatric recipients in North America are older than 35 years of age compared to 19% of donors in Europe ¹⁷.

The ISHLT registry report has identified increasing donor age in adults as a risk factor for higher mortality at 1, 5 and 10 years post-transplant as well as a risk factor for development of CAV within 5 years post-transplant ¹⁸. Reich et al investigated the effect of increasing donor age above or below 50 years and the interaction with ischemic time ¹⁸. The authors divided patients by ischemic time into short (<120mins), medium (120 -240) and long (>240) groups. Five-year survival was reduced in older donors who had medium and long cold ischemic times. However, mortality was no different for older donors with a short ischemic time. Increase in donor age and ischemic time still provided reasonable 5-year survival in adults, around 70% compare with 80% in those with short ischemic time. This reduction in survival is likely to compensate for the increase waitlist mortality due to the shortage of younger organs.

In children, Westbrook et al queried the UNOS database to determine the post-transplant survival of weight-matched controls with a donor age difference of more or less than 5 years ¹⁹. There was a significant difference in survival in those children who received a donor organ that was > 5 years older than their chronological age. This was particularly relevant for those recipients' ages 11-17 receiving hearts from donors who were ≥ 25 years of age.

In those recipients receiving a donor greater than 25 years old, mortality was significantly worse at 10 years when compared with those patients receiving a donor greater than 5 years older but < 25 years (60% vs. 44%) In addition, those patients receiving a donor >5 years older, also developed CAV earlier. Freedom from CAV at 10 years post-transplant was 72% in those with a donor age within 5 years compared to 56% in those with an older donor ¹⁹.

An interesting report by Weber et al. examined a large group of adult transplant recipients receiving donor hearts aged 18-39 and compared them to older donor groups (age: 40-49, 50-54 and ≥ 55 years)²⁰. The authors identified increasing mortality with older donor age with a hazard ratio of 1.4 for recipients with a donor ≥ 55 years. The authors performed propensity matching for recipients receiving donor hearts greater than 55 years with those listed with high urgency for heart transplant (status 1A). Survival was better for those patients prioritized for heart transplant even when transplanted with an older donor. However, when donor age was used as a continuous variable, it was not identified as a risk factor for either mortality or CAV. This lack of predictive value differs from studies selecting an arbitrary age threshold ^{21,22}. In addition to survival, co-morbidities such as cerebrovascular accidents were seen more frequently in the older donor age group, potentially reflecting the state of vascular morbidity in older donors.

From the available evidence the impact of increasing donor age on post-transplant mortality and development of CAV is not universally corroborated. Comparable arbitrary age cutoffs have not been standardized and donor age as a continuous variable in multivariate analysis does not stand out from other important risk factors for recipient survival or development of CAV. It seems reasonable to conclude that increasing donor age is an important risk factor for transplant survival and using donor hearts greater than 50 years requires careful consideration of the relative risk and benefits of proceeding, as well as the logistics involved, including ensuring that ischemic times are kept short. However, it is important to consider that the differences in survival related to increasing donor age may be outweighed by the mortality seen in children who are waiting for transplant and would benefit from widening the donor pool through the use of older donors.

ABO-I and Outcomes

In addition to expanding the weight range and age to potentially increase the number of donors and decrease the waitlist mortality, another strategy that has been applied to increase the donor pool for pediatric patients is the use of ABO blood group incompatible (ABO-I) donors. ABO-I infant heart transplantation was pioneered at the Hospital for Sick Children Toronto in 1996 ²³ in an effort to overcome the obstacles in infant transplantation. This strategy was found to be favorable with a decline in the waitlist mortality from 58% in 1996 in Toronto to 7-10% after the institution of ABO-I strategy ²³⁻²⁶.

To date there has been no reported difference in post-transplant morbidities or graft survival between children with an ABO-I compared to those with an ABO compatible graft ²⁶. Specifically, there is no significant difference in the 5-year freedom from CAV, moderate acute cellular rejection, renal dysfunction or PTLT.

The positive outcomes reported from Toronto, have been replicated in a retrospective multi-center study of 58 ABO-incompatible transplants performed between 2001 and 2010. Freedom from death or retransplantation was 100% at one year, 96% at 5 years and 69% at 10 years ²⁷. Two patients underwent retransplantation; one for development of refractory hypertrophic cardiomyopathy with mitral regurgitation and the second for chronic graft failure. Two patients died in the follow up period; one due to acute multiorgan failure with systemic infection and the second due to combined cellular rejection and AMR associated with donor specific HLA antibodies and positive lymphocyte crossmatch ²⁷. Of the 13 patients who had peak antibody titers > 1:8 against the donor blood group, six had AMR that was treated with clinical recovery and normalization of follow up biopsies ²⁷.

Current practice defining upper age and titers does vary between institutions and countries. In the United States the acceptance of an ABO-Incompatible donor heart is outlined in a UNOS policy. This policy has recently been revised increasing the isohemagglutinin titers to $\leq 1:16$ and the child now needs to be registered before their second birthday. However, with increasing experience, in other countries where no policy exists the upper titer, upper recipient age and interaction between these two are still being defined.

In summary, the acceptance of ABO-incompatible heart donors has become a widely used approach to increase the donor pool and potentially decrease waitlist mortality for infants and young children, without compromising post-transplant outcomes.

DONOR COMORBIDITIES

Donor Comorbidities:

In addition to donor demographics, the impact of donor comorbidities on outcomes following transplant should be considered when making decisions about donor suitability. This particular section will focus on hypertension, diabetes, anaphylaxis, neoplasia history, and genetic syndromes in the donor.

Hypertension

Currently there are no pediatric studies examining the impact of donor hypertension on cardiac transplant outcomes. While chronic donor hypertension could be postulated to impact both graft function and development of CAV, direct study of this issue is limited by the availability of donor health data and often donor cardiac hypertrophy is taken as a surrogate finding for hypertension. One recent adult single center study demonstrated that donor hypertension as assessed by a health questionnaire correlated with reduced graft survival ²⁸. A separate analysis of the impact of donor renal disease on recipient outcomes, found that donor hypertension was associated with a higher risk of retransplant or death ²⁹.

Diabetes

Donor diabetes may also be a plausible risk factor for graft failure or CAV. Again while no pediatric studies exist, a single center retrospective analysis in adults did show that carefully selected diabetic donors could be used successfully for heart transplant without increased recipient risk ⁷. The authors further demonstrated the insulin-dependent diabetes and diabetes history greater than 5 years were not associated with worse outcomes. However, in a cohort of donors with renal disease, diabetes was found to be a risk factor for graft loss even though renal dysfunction itself was not ²⁹.

Anaphylaxis

Though the yearly incidence of food anaphylaxis is rare (estimated at 0.0004% of the U.S. population)³⁰ it may be a feature present in a potential donor. There are several reports of donor peanut allergy conferred upon a solid organ recipient, dating back to 1989^{31,32}. The onset of the acquired allergy can be weeks to months post-transplant, and can occur irrespective of age of recipient or organ type. The prominent finding is the occurrence of an anaphylactic or sensitivity reaction in response to ingesting the food, most often peanuts, though reactions to other foods have been reported. These reactions can be transient and resolve over time, however others report that these acquired food allergies remain a life-long issue³³. Given this impact it may be prudent to include this in donor screening and post-transplant follow up.

Neoplasia

While a comprehensive exploration of all other donor comorbidities is not possible in this review, some other pertinent situations were considered. The presence of a donor history of oncologic disease was reviewed as a risk factor for solid organ transplantation using a retrospective review of the Scientific Registry of Transplant Recipients (SRTR) database showed no increased risk of early death or graft loss in recipients of a donor with oncologic history³⁴. Although notably, hematologic and otolaryngologic tumors were associated with decreased recipient survival following heart transplantation³⁴.

The overall paucity of data on this subject prompted the OPTN/ UNOS to establish a Disease Transmission Advisory Committee tasked with producing guidelines on organ acceptance from donors with a positive malignancy history. Their document recommended employing a strategy of utilizing anticipated donor malignancy recurrence-free survival or 'cure' rates as a surrogate marker for transmission risk. 'Low risk' would be expected from donors who are cancer free for at least 5 years with a cure probability of cure >99%; 'intermediate risk' would be those with a 90-99% cure rate; and 'high risk' would be associated with incurable cancers, insufficient follow up or cure probability <90%³⁵. Additional consideration should be given to the metastatic potential of the donor's current or prior malignancy. In general, however, considering the overall limited data and near absence in the pediatric population, there is insufficient

data to make any meaningful recommendations for the pediatric donor with a history of or active malignancy.

Genetics

Finally, and pertinent specifically in pediatrics, the presence of genetic syndromes in donors has been reported in a series of two cases, one in a donor with Trisomy 21 and another with Turner Syndrome. While both transplants were reported to be a success the authors warn of increased surgical challenges that should be planned for when accepting such organs ³⁶. In addition, understanding the natural history of the genetic condition, including the potential effects on the heart are essential to avoid any long term complications.

DONOR INFECTIONS

Donor infections represent another category of donor co-morbidities that may impact transplant outcomes. This is because a variety of infections (viral, bacterial, fungal and others) can be transmitted through organ transplantation ³⁷. Transmitted infections have the potential to cause significant morbidity and mortality in solid organ transplant recipients despite donor derived transmission being reported in less than 1% of donors ^{38,39}. Variable rates of transmission may be due to the pathogen inoculum, the organ being transplanted and the extent of immune suppression ³⁸. Families of transplant candidates should be informed in advance that despite comprehensive screening, no individual test can fully eliminate the possibility of transmitting an infection ⁴⁰. International organ procurement organizations have developed definitions of “increased risk” donor to help aid in the identification of risk to the recipient at the time of transplant ^{41,42}.

The risk of transmitting HBV, HCV and HIV can be reduced by a thorough donor history combined with serological testing of the prospective donor. However, donor history may be inaccurate or incomplete, as it may come from a third party that lacks full knowledge about risk behaviors. Although donor to recipient infection can still be transmitted despite negative serology and nucleic acid testing (NAT) due to a

“window period”, the risk of HIV and HCV transmission is significantly reduced when both serology and NAT are negative ⁴³. This type of testing also potentially increases organ utilization from NAT-negative, increased-risk donors ⁴².

Hepatitis B virus

Standard risk donors who are negative for all 3 serological tests and those who have been vaccinated identified through HBsAB positivity alone can be used for all recipients. Donors who are HBsAg negative and HBcAB positive may have resolving acute infection, remote infection or (rarely) occult chronic infection, or this result may also be a false positive ⁴⁴. NAT may be helpful and decisions about using a donor with this profile need to be made after individualized assessment of the risks and benefits, in conjunction with an expert. Heart transplant recipients who are immune prior to transplantation are at significantly decreased risk of transmission ^{44,45}. Donors who are HBsAg positive likely have active infection. There is limited data about whether pretransplant vaccination and post-transplant HBIG with antiviral prophylaxis can prevent HBV transmission from HBsAg donor hearts. While this approach it is generally not recommended, consideration should be given to this approach in emergent settings in low prevalence areas after an individualized assessment is performed in conjunction with an expert ⁴⁴.

Hepatitis C virus

Standard risk donors who are HCV seronegative can be used without further testing. NAT testing should be performed in HCV AB positive donors, and a significant proportion will be negative, indicating no active infection. A very high proportion of HCV NAT positive donors will transmit infection to the recipient ⁴². Decisions about donors who are NAT positive should be made in conjunction with an expert to consider if the recipients would be eligible for direct acting antiviral therapy to treat transmitted HCV infection. Currently, direct acting antiviral therapy for HCV is approved for children >11 years of age, although its efficacy has not been evaluated in pediatric heart transplant recipients of HCV infected donors. Data in adult heart transplant recipients to support the use of HCV NAT positive organs is emerging ⁴⁶. It is likely that newer antiviral agents and approval of agents for a wider spectrum of pediatric patients will modify clinical protocols in coming years.

HIV

Currently, HIV positive donors should never be used for non-HIV positive recipients. HIV positive donors can be considered for HIV positive recipients within appropriate research programs with availability of experienced experts although this has not been evaluated in pediatric heart transplant recipients.

HTLV-1

HTLV-1 is endemic in certain populations and can be transmitted by organ transplantation. HTLV-1 screening of donors should not be undertaken due to the risk for organ wastage with high risk of false positive results, low prevalence of HTLV-1 and lack of availability of reliable testing. The value of screening donors from populations with a higher prevalence is uncertain ⁴⁵.

Parasitic infections

Parasitic infections have been routinely reported as donor-derived infections and identification of infected donors with appropriate empiric prophylaxis/treatment is the mainstay of management.

Toxoplasmosis

Empiric prophylaxis has been shown to decrease the risk of Toxoplasmosis in recipients receiving seropositive donor hearts ⁴⁷ although breakthrough infection can occur despite prophylaxis ⁴⁸. Studies differ on the impact of donor/recipient mismatching and outcome for Toxoplasmosis. In the United States, a single institution showed a trend toward increased mortality in toxoplasma donor seropositive, recipient seronegative (D+/R-) patients compared to those not at risk (D-/R-) ⁴⁹. However, two other large European studies reported no difference in all-cause mortality across D/R serostatus pairs (D+/R-, D+/R+, D-/R+ and D-/R- patients) ^{50,51}. Toxoplasma seropositivity in the donor is NOT a contraindication to donor utilization in pediatric heart transplantation. If either the donor or recipient is seropositive, appropriate prophylaxis should be administered to decrease the risk of symptomatic disease.

Strongyloides

Donor derived infections from *Strongyloides* have been reported in adult and pediatric transplant recipients including patients following heart transplantation ^{52,53}. Initially, case reports stemmed from serious and even fatal *Strongyloides* infections that were identified through retrospective assessment revealing negative pre-transplant recipient serology with positive donor serology ⁵⁴. More recently, screening of at-risk donors has become more common allowing for identification in the donor and mitigation in the recipient with pre-emptive therapy ⁵⁵⁻⁵⁷.

Chagas

Trypanosoma cruzi, the etiologic parasite causing Chagas disease, is endemic in Central and South America that can cause a chronic infection involving the heart or gastrointestinal tract. Transmission of Chagas disease from donors to recipients has been documented in solid organ transplantation and occurs more commonly in heart transplantation compared to other solid organs ^{58,59}. At least one transmission from a donor to an adolescent recipient has been documented with evidence of infection by three weeks post-transplant ⁵⁹. Currently, based on the increased risk for infection and associated morbidity and mortality, the WHO, Spanish and United States Consortia all advise against the use of heart donors who are seropositive for *T. cruzi* although other organs from these donors can be considered ⁵⁸⁻⁶⁰.

Malaria

Plasmodium falciparum has been transmitted to an adult heart transplant recipient from a donor from an endemic country despite negative peripheral smear at the time of transplant. Retrospective serology revealed the donor had been previously infected. Treatment with erythropheresis, quinine, artesunate and atovaquone-proguanil was successful ⁶¹.

Bacterial infections – bacteremia, meningitis, pneumonia & tuberculosis

Bacterial infections occurring in potential donors complicate the decision regarding suitability of a donor for pediatric heart transplantation. Donors with a variety of infections including any culture positivity and meningitis have been reported without significant impact on outcomes in adult heart transplantation ^{62,63}. In pediatrics, only 3 proven or probable donor derived disease transmissions related to bacterial

infections (all *Staphylococcus species*) were reported in over 5000 pediatric donors in the United States, and there were no deaths attributed to these transmissions ³⁹. More specifically, Amdani et al. reported on pediatric heart transplant recipients from blood culture positive donors showing there was no difference in survival or post-transplant complications with these donors compared to donors with negative blood cultures ⁶⁴. However, with the emergence of multi-drug resistant (MDR) organisms, transmission from donor to recipient of these difficult to treat organisms has been reported in adult heart transplantation ⁶⁵, although organs from donors with some MDR organisms including carbapenamase-resistant *Klebsiella pneumoniae* have been safely used in at least one adult heart transplant recipient with targeted peri-operative and post-operative antimicrobial administration ⁶⁶. To date, no pediatric reports using donors with MDR bacterial infections appear in the literature and donors with these organisms should be considered with caution focusing on the therapies available to treat a recipient should a donor-derived infection develop.

Additionally, transmission of *Mycobacterium tuberculosis* (TB) from a donor has been reported in adult heart transplantation ⁶⁷; however, medical management of the recipient prevented TB-related morbidity and mortality despite documented transmission. Review of the literature in solid organ transplantation suggests increased risk of TB in donors from or traveling to endemic countries, with prior latent TB infection, active tuberculosis and known socioeconomic risk factors including homelessness and incarceration ⁶⁸.

Fungal Infections

Fungal infections in potential donors also pose risk to recipients with significant mortality if unrecognized and untreated in the recipient post-transplant ⁶⁹. The mechanism of donor death must also be considered with reports of fungal infections including *Scedosporium auratiacum* in an adult heart recipient from a donor who drowned ⁷⁰. Very early onset (<30 days post-transplant) infection with *Cryptococcus* has been reported in two heart transplant recipients which may represent either unrecognized infection in recipient pre-transplant or in the donor ⁷¹. Unrecognized infection especially in donors from regions with endemic fungi like coccidioidomycosis appears in the literature and includes pediatric heart transplant

recipients ^{72,73}. Prophylaxis and early therapy decrease the risk for mortality of coccidioidomycosis post-transplant ⁷⁴.

Other viral infections (Dengue)

Transmission to heart transplant recipients in endemic areas has occurred with Dengue virus and West Nile Virus. At least 4 recipients including one heart transplant recipient contracted Dengue virus from two donors in Brazil ⁷⁵ causing clinical illness post-transplant without deaths. However, transmission of West Nile Virus from donor to recipients has been reported to cause neuroinvasive disease in up to 70% of recipients and death in 30% ⁷⁶. Although donor derived infection has not yet been reported in the literature for Zika virus, a survey of donors from an endemic area indicate that 3% were positive for Zika IgG but none were positive by PCR testing ⁷⁷.

Encephalitis & Amebiasis

Donors presenting with non-bacterial meningoencephalitis have been reported to transmit a variety of infections in solid organ transplant recipients not previously covered in prior sections including but not limited to Rabies and Balamuthia mandrillaris ⁷⁷⁻⁷⁹. It is recommended by the Ad Hoc Disease Transmission Advisory Committee of the United Network for Organ Sharing in the United States that donors with meningoencephalitis due to a pathogen without available treatment that extreme caution be used in determining the suitability of the donor based on the events reported to this committee

(<https://optn.transplant.hrsa.gov/resources/guidance/guidance-for-recognizing-central-nervous-system-infections-in-potential-deceased-organ-donors/>).

Summary Statement

There are a number of donor characteristics that potentially impact outcomes following pediatric heart transplantation. However, we acknowledge that there are many factors that may affect the potential outcomes following heart transplantation and these need to be taken into consideration along with their interactions with donor demographics and co-morbidities. The following is a list of specific considerations with respect to donor characteristics that may be considered at the time of an offer:

- 1) A donor recipient weight ratio between 0.7 and 3 should be considered when assessing a donor offer
- 2) Donor age <50 years should be considered, however this needs to be assessed in the context of the ischemic time, with longer ischemic time impacting recipient survival when older donor hearts are utilized
- 3) ABO-I donors should be considered in patients that are eligible, as the outcomes have been shown to be equivalent to ABO-C patients
- 4) Little is known about the impact of donor comorbidities on the outcomes post-transplant in children
- 5) It is essential to be aware of the potential infections in the donor, understand the appropriate testing required to identify an infection, have a good understanding of the potential risks of transmission from the donor to recipient and be aware of available treatment options for the recipient post -transplant before accepting an organ.

Future Research

In order to move the field forward and impact the utilization of the donor pool, future research is required to understand the impact of interactions between various donor characteristics and donor and recipient characteristic on outcomes to aide in decision making about donor acceptance. Lastly, being able to define how we can push the boundaries with ABO-I transplants has the potential to further increase utilization.

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