Pediatric heart transplant is used as a next step in palliation for children with heart failure refractory to other medical therapy. Current outcomes of all pediatric patients who undergo transplant has improved significantly since the initial transplant in 1967. In the current era, the 1- and 5-year survival are approximately 90% and 80%, respectively (1). However, the waitlist mortality continues to remain high. An analysis of the US Scientific Registry of Transplant Recipients (SRTR) database demonstrated that the overall 1-year mortality for all listed patients while waiting was 17% (2).

The size of the active waitlist for pediatric patients increased by >20% between 2010 and 2014 (3). As the number of patients placed on the transplant waitlist continues to grow, the number of pediatric heart transplant has been steady during this time (4). As a result, the percentage of patients transplanted among those on the waitlist has continued to decline. When looking at organ utilization in the same era, only 32% of all available donors and approximately 50% of pediatric donors were used for heart transplantation in 2014 (5).

Donor characteristics are used to determine acceptance of organs. Historically donor characteristics such as decreased ejection fraction, presence of cardiopulmonary resuscitation (CPR), prolonged CPR, predicted prolonged ischemic time, mechanism of death were thought to signify “marginal donors”. This term is used to qualify donors who have characters which may lead to poor recipient outcomes. However, there is not enough evidence to substantiate such beliefs, and more recently, organ utilization has been evaluated further in hopes to expand the donor pool in order to match the growing waitlist (6-9). Furthermore, when looking at donor offers declined for organ quality, pediatric recipients that received hearts refused multiple times by other centers had similar outcomes to those recipients who had none or fewer refusals, even for the high-risk recipients (10).

In this review, we will discuss factors that are commonly reviewed when considering a donor offer for pediatric heart transplantation, in the light of recent literature.

**Donor age**

Donor age is considered a risk factor of poor post-transplant outcomes in the adult heart transplant field (11). However, when reviewing older donor offers the decision is likely dictated by comorbidities typically seen in the older population (e.g., coronary artery disease, and smoking history). Although possible, these comorbidities are uncommon in pediatric field. A recent study by Westbrook...
et al. studied outcomes stratified by donor-recipient (D-R) age difference. They showed that a D-R age difference of >5 years was associated with decreased post-transplant survival, and increased coronary allograft vasculopathy. Of note, the increase in mortality was primarily contributed by the adolescent cohort receiving a donor heart from individuals >25 years of age (12).

**Donor size—weight/ height/ BSA or virtual fit**

The donor-recipient body weight (DRWB) ratio is the most common method to determine acceptable donor weights for recipients, which among other factors creates a range for possible donor offers for the candidates. This ratio does not incorporate actual cardiac volumes, which has shown to limit possible donors. More strikingly, these DRWB ratio vary significantly from program to program and even within a program without any consistency (13,14).

More recently the concept of virtual fit using 3D printing has emerged as a tool to continue to expand possible donors. A recent study by Szugye et al. compared their standard donor-recipient body weight-based listing (1:1 to 1.5:1) to chest computed tomography scans (CTs) of dilated cardiomyopathy patients which had been obtained as part of routine imaging prior to transplant and then later converted to 3D imaging analysis. They found that virtual transplantation was able to allow for a wider range of weights when compared to their standard weight-based listing, overall allowing for individualized size matching (15).

Additional work done by Plasencia et al. used virtual fit to aid clinicians in predicting potential compression effects from donor offers, with the goal to expand potential donor offers by accepting “oversized” donors (16). Two methods were used: First was a healthy heart library to derive a suitable donor to match the organ offer and the second method utilized actual donor images to create a real-time 3D visual assessment of fit. The heart health library used linear regression model of normal heart reconstructions offers based on CT/MR images to determine total cardiac volume (TCV) to develop and validate a linear regression model that predicts a healthy allograft TCV. They reported a total of 3 cases, where DRBW ratio was in the range of 2–3 (unacceptable in many programs); however, the actual TCV ratio was 1 or less and their program proceeded with transplant without any complications. These studies and other current efforts in the field will provide standardized, evidence-based tools that could determine “safe” upper limits of potential donor size and move away from an archaic method of predicting appropriate cardiac size.

**Mechanism/cause/circumstance of death**

Donors’ mechanism or cause of death is generally not a concern where complete information about organ function and anatomy is available. However, situations with incomplete cause of death data still exist: in blunt trauma victims where, cardiac contusion cannot be ruled due to insufficient imaging or laboratory data, or transmittable disease status (especially HIV) in drug overdose cases to just describe a few. In such situations, decisions are dictated by recipient factors, likelihood of waitlist survival, and the assessment of donor retrieval teams. Of note, cases where the cause of death is unknown, such as in the case of an otherwise healthy child who was found unresponsive (SUID), careful cardiac and genetic considerations are warranted to ensure successful transplantation.

CPR and duration of CPR have been a point of contention among providers making decisions about donor offers (13). Several studies have demonstrated that the presence and duration of CPR have no influence on short- or long-term posttransplant outcomes (17-19). Of note, these studies did not analyze all donors resuscitated beyond 30 minutes in their study population. Therefore, any resounding conclusions regarding the effect of extended CPR on posttransplant outcomes are challenging to make.

**Ejection fraction**

Similar to general practice, normal ejection fraction is commonly defined at ≥55% for donor hearts. This information is reviewed and is a significant part of decision making at the time of donor offer. Donors with reduced ejection fraction have been cautiously used in pediatric patients due to the belief that decreased ejection fraction implies poor organ function and may cause poor transplant outcomes. However, it is important to realize that echocardiographic evaluation is generally performed in a setting where cardiac function is influenced by an “autonomic storm” secondary to brain death. This is commonly referred to as “neurogenic stress cardiomyopathy in heart donors” (20). In these cases, a depressed left ventricular (LV) function is likely transient in an otherwise healthy individual. This phenomenon was demonstrated by Madan et al. in a study that compared donor hearts with transient left ventricular systolic dysfunction (measured on multiple echocardiograms during donor management)
with donors with normal LV function at baseline. This study primarily studied the adult population but found that the group with transient LV dysfunction was significantly younger (median age of 25 vs. 30). Post-transplant outcomes were similar in terms of 30-day, 1, 3, and 5 years mortality (21). These findings were supported by other similar studies (22).

In pediatric heart transplantation, literature regarding the effect of low ejection fraction has been inconsistent. Some studies reported low ejection fraction as an independent predictor of post-transplant 1-year mortality whereas, a study by Rossano et al. found that recipients who received hearts with depressed function had similar outcomes to those whose donors had a normal ejection fraction, regardless of the degree of dysfunction (8,23). A consistent finding from these studies was that donors with sub normal ejection fractions were rarely utilized.

Even with studies showing similar outcomes despite donor LV dysfunction, a high percentage of organs are still not utilized. UNOS review from 2007 to 2014 of donors between 13 to 58 years of age showed that about 20% of potential cardiac donors are excluded due to LV dysfunction (24). Given the increasing literature showing similar outcomes of recipients who receive heart donors with reduced ejection fraction, there is a potential to significantly expand the donor pool and therefore decrease waitlist mortality.

**ABO incompatible**

Infants and children often have longer waitlist time compared to older children given limited donor availability for their size and age, even when listed as highest priority for an organ. Generally, blood types must be matched between recipient and donors. One advantage in young infants and children however is the presence of an immature immune system and their inability to produce adequate levels of isohemagglutinins (anti-A or anti-B) until the age of 12 to 14 months. This allows for the option to accept hearts across blood types. As a result, centers have been using ABO incompatible (ABOi) heart transplants to optimize donor options. The first ABOi transplant was performed in an infant in Canada in 1996 (25). Since then studies continue to show equivalent outcomes in infants and young children who receive an ABOi heart transplant and similar freedom from rejection when compared to ABO compatible transplants (26,27). Given these comparable outcomes, more countries are using the option of ABOi heart transplantation.

Most centers perform isohemagglutinin testing in the recipient to assess the presence and concentration of antibodies toward other blood types. Acceptable antibody titers for transplanting across blood groups is <1:16, as recommended by UNOS policy (28). Some centers have reported ABO incompatible transplants with titers ≥1:16. In the United Kingdom, where transplantation across blood types has been performed for longer than in the United States, a report of 12 patients (five of which were >2 years of age) had isohemagglutinin titers of ≥1:16 and were transplanted. Thirty-three percent of these patients had early anti-body mediated rejection within the first 15 days after transplant. Three of the 12 patients died; however, these deaths were not believed to be directly related high isohemagglutinin titers. In regards to overall survival, there was 75% survival in the high titer group versus 89% survival in patients with <1:16 titers (29). The results from ABOi transplants provide careful optimism for a difficult to match recipient population and its broadening use require further investigation.

**Positive crossmatch**

All individuals have a unique set of human leukocyte antigens (HLAs) which are expressed on their tissue and organs, and allow the immune system to recognize self from non-self. Prior to listing for transplant, each recipient is evaluated for antibodies against non-self HLAs. This process of evaluating for antibodies against possible donors in the general community is called panel reactive antibodies (PRAs). If there are preformed antibodies toward potential donors in the community then those donors are avoided in order to prevent hyper-acute and acute rejection of the heart following transplant. If a recipient has a high percentage of PRAs then they are considered sensitized (often >10% is considered sensitized), which is a challenge as it can exclude multiple potential donor options. As a result, children who are sensitized have a longer waitlist duration and increased waitlist mortality (30,31).

Some transplant centers may transplant organs in which the recipient has known antibodies towards a donor, this is known as a positive crossmatch. Outcomes of patients who undergo positive crossmatch have shown higher risk of post-transplant mortality. A review of the UNOS data registry showed that an elevated PRA was associated with overall worse post-transplant mortality (32). Further study by the clinical trials in organ transplantation in children
(CTOTC) program used a prospective, multi-institutional observational cohort study design to assess the impact of pretransplant sensitization. A total of 54% were considered sensitized by their criteria and were found to have less freedom from acute antibody mediated rejection as well as cellular rejection. However, freedom from death, retransplantation or rejection with hemodynamic compromise at 12 months were comparable (33).

The question remains, what are acceptable outcomes for transplant in this setting and when is it worth the risk to perform a positive cross match transplant? More work is needed in this area to determine the safety of these types of transplant and their impact on outcome in the immediate post-transplant course and more importantly in the long term.

**Ischemic time**

Longer donor ischemic time is shown to have significant impact on post-transplant morbidity and survival (23,34,35). Offers where expected ischemic times are greater than 4 hours usually encourage teams to carefully consider other recipient factors such as chances of waitlist survival, diagnosis, etiology of cardiac decompensation, presence of PRA, donor-CPR time, and ejection fraction in their decision making. Additionally, it also informs the decision to increase the frequency of post-transplant surveillance. Furthermore, there is growing evidence about the use of ex-vivo perfusion for supporting organs with prolonged ischemic time and can potentially reduce or eliminate this consideration in the future (36).

**Donor scoring systems**

In the current system, donor evaluation is largely a subjective and qualitative process. In contrast, kidney transplantation follows a highly quantitative method of evaluating multiple donor factors using standardized tools such as the kidney donor risk index (KDRI), which not only informs decision making but has shown to positively impact outcomes (37). There is a significant amount of variability in donor acceptance practices at different pediatric heart transplant centers which contributes to poor donor utilization and makes studying outcomes challenging (38). Several groups have made strides toward developing a tool that could address this issue; however, it needs further improvement and validation to be introduced into practice (23,39). Another concept that is being studied by our group is whether a risk-based donor and recipient matching will allow for better organ utilization and improve the total number of post-transplant years achieved for the entire transplant population.

Donor evaluation for heart transplantation is a complex multi-step process and requires consideration of many recipient and donor factors, some of which are not discussed here. Given the growing waitlist, donor shortage is a cause for concern and the transplant community is increasingly focused on methods to improve donor utilization, which could mean expanding some of the criteria discussed above.

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**Footnote**

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**References**


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