Review Article

Ethical issues in access, listing and regulation of pediatric heart transplantation

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Abstract: Organ scarcity often drives ethical discussion in pediatric heart transplantation. There are questions about autonomy and equity in the referral patterns. There are questions about beneficence in how referral centers are established and operate. There are questions about fairness in how patients are listed and evaluated for listing exceptions. Finally, there are questions about beneficence, maleficence, and justice when it comes to the regulatory oversight of transplantation. This review will serve as a brief review of some of the more pressing ethical matters in pediatric heart transplantation and, where possible, offer potential solutions.

Keywords: Ethics; heart transplant; pediatrics; regulation

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Introduction

"*Drawing from regulatory guidance and ethical principles, we find that there is a reasonable basis for giving preference to pediatric transplant candidates for allocation*." (1).

Since the very first pediatric heart transplant in 1967, when Dr. Kantrowitz and his team gave new life briefly to an 18-day-old New York baby (2), there have been ethical questions, dilemmas and quandaries in the field. Many of these issues are not exclusive to pediatrics or to heart transplantation. Medical futility, the idea that no matter the interventions available modern medicine cannot always prevent death, continues to be an issue with patients too sick to undergo transplant. Informed consent, the driving force behind the autonomy of patients in medical decision-making, remains an elusive ideal from an ethical standpoint and a barebones necessity from a legal perspective. While entire books have been devoted to topics such as these (see Zucker & Zucker 1997 (3), Faden & Beauchamp 1986 (4)], this review is meant to briefly examine a few issues specific to pediatric heart transplantation particularly relevant to the field today: access, listing, and regulation.

Access to pediatric heart transplantation

In principle, every child with end-stage heart disease has the right to heart transplant. In practice, there are insufficient organs to accommodate the demand. There are logistical challenges to allocating organs and reduce ischemic time. There are scenarios when the risk of heart transplant outweighs the benefit that might be achieved in one patient (someone who is deemed "too sick"), if compared to the use of that organ for another patient. Ethical matters related to access to heart transplantation (which could apply to other pediatric organ transplants) include referral patterns, the scarcity and the expertise of centers.

Access to heart transplantation first involves a referral. There continue to be barriers to referral, which inevitably leads to questions about justice and fairness. Some referral differences are related to lack of data or education on the part of the referring providers. For instance, timing of referral for children with single ventricle physiology status-post Fontan has been a challenge. Simply defining Fontan failure has been difficult with suggestions that include low cardiac output in the absence of ventricular failure (5), myocardial

failure (6), "death, (Fontan) takedown, transplantation, or New York Heart Association (NYHA) classes III and IV (heart failure)" (7), as well as separate phenotypic failure mechanisms of reduced ejection fraction, preserved ejection fraction, abnormal lymphatics and normal hemodynamics (8). Because of the diagnostic variability, it remains difficult to determine optimal referral timing for this group. One way to limit discrepancies for referrals, is through consensus building. An example for the Fontan population, is a referral document created and distributed by ACTION (Advanced Cardiac Therapies Improving Outcomes Network) (9). Other instances are subtler and may be more difficult to track. For instance, referral patterns for children with end-stage heart failure and developmental disability or significant genetic abnormalities may be systematically low. While the evidence is lacking (it's hard to track inappropriate non-referrals), one case series may highlight the problem. A large adult and pediatric heart transplant referral center in England saw only one referral with Down syndrome among 800 total referrals over a 14-year period prior to 2000 (10). The authors noted "the paucity of referrals is surprising given the high prevalence of Down's syndrome and associated cardiac problems". Further, there may be some reluctance among referring providers based on historical trends of heart transplant providers weighing neurodevelopmental delay when evaluating for transplant (11). While there may be fears about poor clinical outcomes related to non-adherence to medication regimens or inability for self-care, there has been no evidence that they experience worse outcomes (12). A few high-profile media reports over the last few decades highlight these very issues. In 1995, a 34-year-old Sandra Jensen needed a heart-lung transplant but was initially denied based on her extra chromosome and developmental delay (13). Paul Corby, a 24-year-old with severe autism, was denied listing for heart transplant at three centers, all with concerns about his ability to care for himself despite overwhelming family support (14). And another, Maverick Chenkus, a little boy with hypoplastic left heart syndrome and rare genetic syndrome was denied listing for a heart transplant because, as his parents claimed, of his presumed future disability (15). The challenge to respect the autonomy of families wanting transplant for their child in the setting of scarce resources will remain an ethical dilemma.

What about the centers to which a potential recipient is referred? Across the United States, there were 58 centers where pediatric heart transplants were performed from July 2017 to June 2018 (16). Of those, 24 centers did five or fewer heart transplants during that yearlong period, while only 18 centers performed in double digits. This makes pediatric heart transplantation a relatively rare event. Because of its rarity, there is an argument that fewer centers performing more heart transplants is better than more centers doing fewer transplants. There is evidence that waitlist outcomes in low-volume pediatric heart transplant centers is inferior to high-volume centers with center volume noted to the most significant risk factor for waitlist death (17). This is not an isolated argument to pediatric transplant, though. A United Network of Organ Sharing (UNOS) registry study using pediatric and adult cardiac transplant centers (18) and a later systematic review (19), both showed a relationship between low-center volume and worse post-transplant survival. However, restricting pediatric heart transplants to only "high-volume" centers would limit the geographic realities for families. In fact, based on the 2017 to 2018 fiscal year numbers, restricting transplants to centers that perform at least ten per year would mean families from 34 states would need to travel out of state. Is that a worthwhile trade-off? A natural follow-up question is whether distance from center matters. A single-center study of a large adult center showed that graft failure and mortality were associated with increasing distance from their center (20). However, a pediatric-focused registry study showed no difference in survival between heart transplant recipients travelling less than 20 miles and those travelling >100 miles for care (21). While centralizing care may not obviously affect survival, there are many other factors to consider such as temporary relocation, disruption of support networks, separation of families, travel and all the associated costs. When the goal is to put the patient first, the decision to refer, referral timing and where to refer (aside from health insurance meddling) lead to tough questions and often tougher answers.

Listing of pediatric heart transplant candidates

Once a child with end-stage heart failure is deemed a candidate, listing priority poses a new series of challenges. All these challenges would be irrelevant if there were sufficient and timely organ availability for all transplant candidates. Unfortunately, cardiac donors, especially ones with the right size and blood type, are significantly rarer than the number of children who need heart transplants. Because of this supply-demand mismatch, an allocation system was developed by UNOS to prioritize the sickest children (those in the hospital, usually on IV medications or

mechanical support). What must also be remembered is that "the organ is a precious resource which, if not efficiently used, is lost to another potential recipient" (22). Therefore, specific listing criteria based on severity of illness were developed in 1999 and recently revised in 2016. While these criteria try to capture the breadth of cardiac diseases and their associated risk of morbidity and mortality, the reality is that children with end-stage heart disease are a very heterogenous group. For this reason, status exceptions are allowed. This is a petition written by the listing team to advocate for higher priority status, despite not meeting the defined criteria, because of the belief that the child's risk is equivalent to the higher status group. This process, however, is not perfect and may in some instances be lacking in the equipoise it is trying to create.

The exception process is not standardized or transparent. Additionally, there is conflicting evidence to the overall benefit of status exceptions. Godown *et al.* examined status exception use by UNOS region and found significant variability ranging from 0.7% to 16.4% of status 1A candidates listed by exception for pediatric heart transplant (23). Waitlist survival was comparable to those listed status 1B and significantly better compared to those listed by standard criteria for 1A. In a separate study, Davies *et al.* also reviewed outcomes for pediatric patients listed by status exception compared to those listed by standard criteria (24). Interestingly, they found no difference in waitlist mortality compared to those listed by standard criteria but did find inequity in the process with listed patients from low socioeconomic backgrounds less likely to be listed by exception. Additional information regarding the use of status exceptions after the latest criteria change in 2016 have not been elucidated. Preliminary work, though, suggests status exceptions are significantly increased over the last couple of years (6% *vs.* 19%, P<0.01) since the changes were implemented (25). A significant minority of the new status exception requests are for children with dilated cardiomyopathy, who may have been previously been captured under old 1A criteria (4% *vs.* 30% of total exceptions, P<0.01). Another concern is the way status exceptions for pediatric heart transplant listing are reviewed. Currently, the process involves a heart-specific review board in each region that evaluates each case. There is no standardization of the make-up of the board and most often consists of either majority or entirely of adult cardiologists or cardiothoracic surgeons. There is limited consistency and complete lack of transparency as each board operates independently and without public scrutiny. One seemingly simple solution is to create a national pediatric-specific, heart-only review board. This would "eliminate the need for adult-trained physicians", "great(er) transparency", and "help to standardize the use of pediatric (status exceptions) across UNOS regions" (26).

Another ethical question that is starting to surface is the listing status of children on ventricular assist device (VAD) support. Current listing criteria allow for any patient less than 18 years old that "requires assistance of a mechanical circulatory support device" may be listed status 1A (27). Based on the Berlin EXCOR® data, which early on showed a stroke rate of 29% (28), and more recent data suggesting it is still around 20% (29), this is likely reasonable for this group. However, patients on Berlin VADs are confined to hospital admission, partly due to the precarious clinical status but also due to the non-portable nature of the IKUS driver. Studies focusing on larger and older children who are more similar in size and weight to adults, and that receive adult-size continuous-flow VADs do not have that same risk profile (29). In fact, waitlist mortality and post-transplant outcomes have shown a significant improvement with the increased use of VAD in this population, especially those with favorable two-ventricle anatomy such as dilated cardiomyopathy. This is the group of patients that can be and, in about half of cases, are being discharged from the hospital. Moreover, it is this group of clinically stable outpatient adolescents on VAD support that, at least when comparing to other patients listed status 1A, may not have the same risk profile. There was a similar transition for adult heart transplant candidates more than a decade ago, where stable outpatient VAD recipients no longer required listing at the highest priority without additional clinical or device concerns. Taking into consideration the adult experience and the improving outpatient pediatric experience with VADs, equity may dictate that this group not warrant top listing priority.

Regulatory oversight

The systemic ethical shadow overlying the previous issues and affecting pediatric heart transplantation is the regulatory environment within which all United States programs must operate. While UNOS is the obvious regulatory body over solid organ transplants in the U.S, the Centers for Medicare and Medicaid Services (CMS) also play a strong and important role in regulating this field. "*For centers 'on the bubble,' clinical and programmatic decision-making to preserve CMS (or UNOS) certification rather*

than patient-centered care may dominate." (30). In fact, aside from revocation of a member's designation as a transplant program, the biggest threat is often financial with potential for ending Medicaid reimbursement for the transplant program or for the entirety of the hospital system.

As mentioned before, the review board process may not be setup in the fairest fashion and could benefit from both nationalization and transition to expressly pediatric-focused. Another looming challenge is how transplant programs are assessed. The current system emphasizes post-transplant outcomes, specifically survival to one and three years. These metrics, while marginally useful, ignore one half of the survival equation. A program's true survival should really be preventing death from the time of listing. By current standards, pre-transplant (or waitlist) survival is ignored. This system creates at least two problems: (I) risk-aversion with donor acceptance and (II) risk-aversion with candidate acceptance. Risk aversion with donor acceptance comes about because programs are focusing on post-transplant outcomes. One technique a program can use to favor post-transplant survival is to choose only donors that have minimal concerns (i.e, no down time, perfect size, normal function, no infectious concerns). While this superficially is a good thing, this philosophy keeps the waitlist mortality unfortunately high by reducing risks on more marginal donors. This is not just program preference, but essentially a federal mandate as programs are penalized, and can have their transplant privileges revoked, if post-transplant survival (not overall survival) does not meet national standards (essentially >90%). This is only exacerbated by the overall low pediatric transplant numbers. As discussed earlier, most programs are doing fewer than 10 transplants a year, meaning even one mortality puts the program on the edge. The second problem is the risk aversion against candidate selection. Again, because programs must emphasize post-transplant outcomes, if there is a marginal potential candidate there is a disincentive to taking a chance on that child as a recipient. The current model used for calculating expected post-transplant mortality tries to take certain high-risk clinical features into account, but the disincentive remains. This combination leads to a regulatory framework that promotes perfect donor transplants into reasonably healthy recipients, while potentially useful organs are being discarded, potential recipients are being turned down, and programs are systematically limited in their ability to push the boundaries.

Conclusions

Organ scarcity is the root of transplant ethics. If there were enough organs, referral patterns wouldn't lead to judgment on who is or who is not deserving and referring centers would all have enough experiential volume. If there were enough organs to meet the heart failure demand, there would be no waitlist and children could get a transplant when they needed it. If there were enough quality hearts available, it would significantly decrease any need for regulatory oversight. Alas, ethics will continue to play an important role in pediatric heart transplantation because of the lack of available donor hearts. This begs the question, are there ways to refine the system? The answer is assuredly yes. Using ethics as our guide, we can improve access and delivery of care, refine listing criteria, and reform the regulatory environment to best serve this most vulnerable of populations.

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Footnote

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