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Review

# The difficult to transplant patient: Challenges and opportunities

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ABSTRACT

With a rising number of children with advanced heart failure coexistent with advances in mechanical circulatory support (MCS) and medical therapies for heart failure, there is an increase in patients being considered for orthotopic heart transplant (OHT). Given the changing population of potential candidates and the limited supply of donor organs, identification of those children at highest risk for poor post-transplant outcomes is imperative, as are targeted therapies. Recent advances in the use of MCS and an improved understanding of the lymphatic system offer promising options for improved care. This article will review heart transplant as a therapy for end stage heart disease, those characteristics which make patients high risk candidates for OHT, and emerging therapies for those patients who are at the highest risk of poor post-transplant outcomes.

## 1. Introduction

With major advances in surgical techniques, the evolution of advanced mechanical circulatory support, and refined medical management, there is an increasing number of children who are living with advanced heart failure. While orthotropic heart transplant (OHT) is perhaps the ultimate therapy for children with the most severe form of cardiac disease, it is distinct from other types of therapies and many types of solid organ transplant in that it relies on the use of deceased donors. While there is an increasing number of children reaching the point in their care at which OHT is being considered, the total donor pool has remained relatively stable, which has resulted in a growing number of children awaiting transplant [1,2]. This presents a series of unique challenges for the team caring for those patients, as they must balance the primary responsibilities to the patient, along with broader responsibilities to the donor and donor's family, and society as a whole. Integral to negotiating that responsibility is understanding which patients are at highest risk of poor outcomes post-transplant, as doing so allows for prudent listing selection, and ideally, focused and effective therapies for those patients deemed to be at the highest risk. This review will focus on heart transplant as a therapy for end stage heart disease, those characteristics which make patients high risk candidates for OHT, and emerging therapies for those patients who are poor candidates for transplantation.

## 2. Unique aspects of heart transplantation

Since the first successful pediatric heart transplant > 50 years ago [3], OHT has evolved to become a mainstay in the treatments for children with end stage heart failure from congenital heart disease, cardiomyopathy, and acquired heart disease. Unlike bone marrow or some other solid organ transplants such as kidney transplants, OHT relies on the availability of deceased donors. While there has been a persistent increase in the number of children awaiting OHT, the donor pool has remained relatively static, resulting in longer waitlist times [1] (Fig. 1). Awaiting transplant is not without risk, with studies showing an increased frequency of waitlist mortality in infants, and poor long term survival for those pediatric patients awaiting transplant while support on Extracorporeal Membrane Oxygenation (ECMO) or invasive ventilation [4]. With the knowledge that many patients will die while awaiting transplant, the decision of whom to choose to receive the limited supply of organs requires careful consideration.

While OHT is perhaps the ultimate therapy for children with end-stage heart failure, it is not curative. The overall median survival has increased over the past 35 years, though the majority of that impact has been made in the first year after transplant, and even in the current era the age group with the best outcomes, infants, still has a median survival of only 20.7 years [5] (Fig. 2). These findings point out the multiple, and sometimes competing, responsibilities of the transplant team. They have a responsibility to their patient; to give them the best chance of meaningful survival, but they must balance this onus with good

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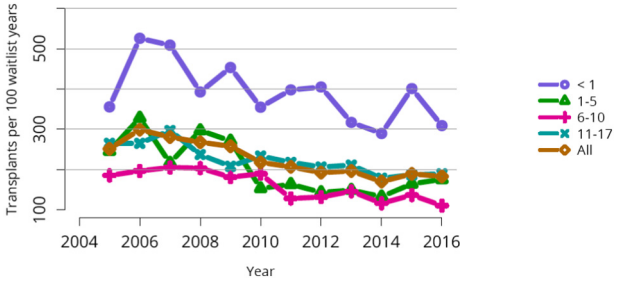


**Fig. 1.** Trends in the number of transplants per 100 waitlist years: With a growing number of children in need of OHT, and a fixed number of available donors, the number of transplants per 100 waitlist years is decreasing.
Colvin M, et al. Am J Transplant. 2019

organ stewardship and the difficult realities of a limited organ supply.

## 3. Factors that influence the likelihood of a successful transplant

### 3.1. Congenital heart disease

Multiple studies have shown that a diagnosis of congenital heart disease (CHD) confers an increased risk of post-transplant mortality [6–10] (Fig. 3). These patients present unique surgical challenges secondary to prior sternotomies and anatomical variances, contributing to increased bleeding and longer ischemic times [11]. Their wait times are often longer, due to being sensitized, which means that by the time of transplant they are frequently deconditioned and have poor nutritional status, risk factors on their own for poor outcomes [12,13]. Survival for patients listed for transplant after a Norwood palliation have particularly poor outcomes, with only 60% surviving to transplant and only 48% still living 1 year after listing [14,15]. Given their complex anatomy, ventricular assist devices (VADs) are infrequently used in this population which further contributes to waitlist mortality, and potentially worse outcomes after transplant. Yet, despite these findings, congenital heart disease is now the leading indication for pediatric OHT, having increased from 45.0% of candidates in 2007 to 57.5% by the end of 2017 [1], and heart failure in the CHD population has been shown to be an important and growing cause of morbidity, mortality and resource utilization [16], emphasizing the importance of improving therapeutic strategies in this high risk cohort.

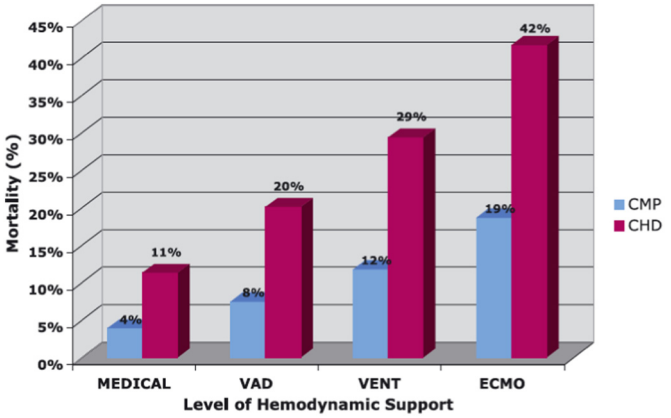


**Fig. 3.** The Impact of CHD: Regardless of the level of hemodynamic support at the time of tranpslant, the presence of CHD is an independent risk factor for post-transplant death.
Almond CS, et al. Am J Transplant. 2012

**Table 1**
Commonly Identified Risk Factors for Poor Post Transplant Outcomes.

| |
|---|
| Congenital heart disease |
| Impaired end organ function: *Abnormal Bilirubin*, *Abnormal Creatinine* |
| ECMO support at the time of transplant |
| Invasive ventilation at the time of transplant |
| Panel reactive antibody (PRA) value > 10% |
| High risk social situations |

### 3.2. Organ dysfunction

Patients who go into transplant with impaired end organ function have worse post-transplant outcomes, with abnormal bilirubin and creatinine clearance both shown to be independent predictors of poor outcomes [9]. The use of ECMO as a bridge to transplant, or invasive ventilator support has also been shown to correlate with lower rates of survival after transplant [9,17,18]. These results highlight one of the biggest challenges in pediatric heart transplant medicine. The natural human inclination, and the process by UNOS allocates organs, is to offer the donor heart to the sickest recipient. However, it appears that there may be some patients who are so sick that they are unable to make good use of the organ, unless they can demonstrate some recovery of end organ function.

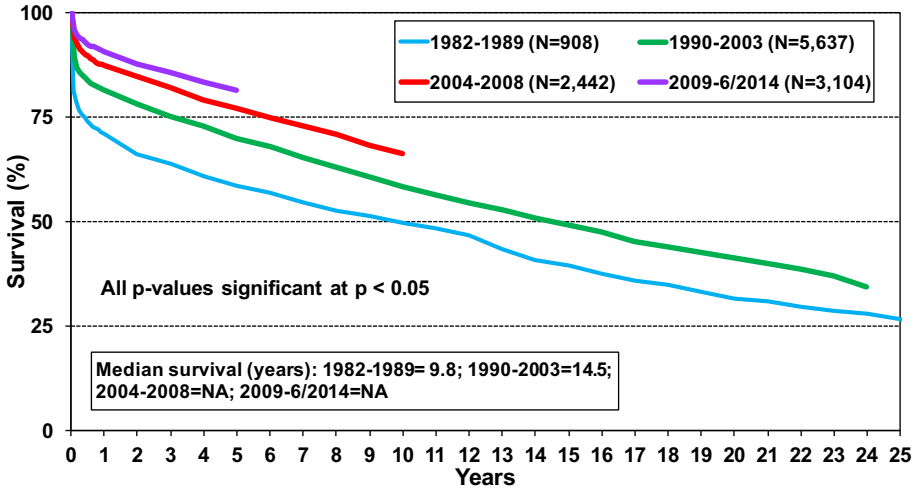


**Fig. 2.** Trends in survival by era: Overall post-transplant survival has improved, though the slopes of the survival curves after the first post-operative year remain fairly similar across eras.
Rossano JW, et al. J Hear Lung Transplant. 2017

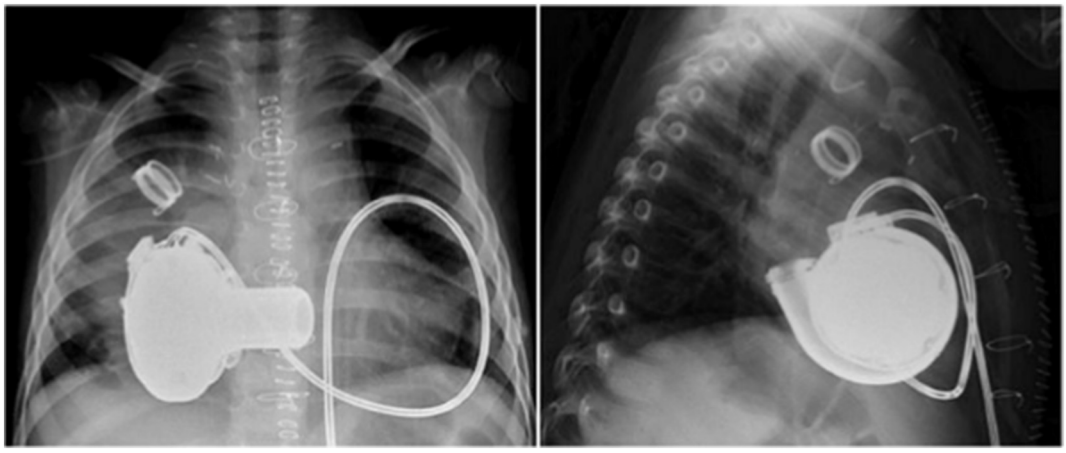

**Fig. 4.** Creative strategies for VAD implantation: A chest radiograph of a 3.7 kg child with Fontan physiology after implantation of a continuous flow VAD in the common atrium with simultaneous excision of the AV valve.
Nandi D, et al. Ann Thorac Surg. 2018

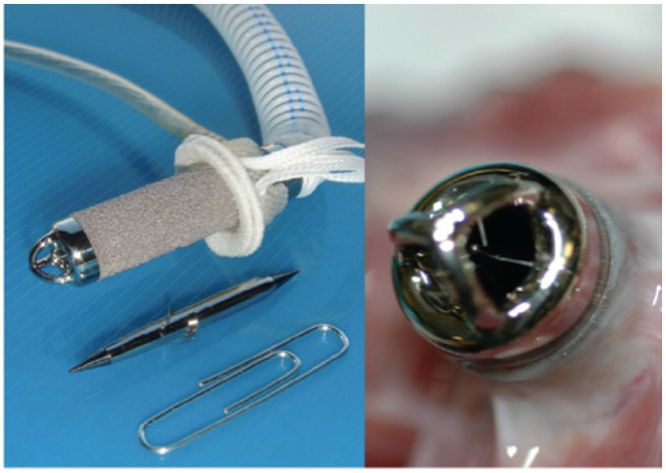

**Fig. 5.** Infant Jarvik: The PumpKIN trial is designed to evaluate the safety and potential benefit of the Infant Jarvik, a miniaturized continuous flow VAD designed specifically for pediatric patients.

### 3.3. Sensitization

Anti-human leukocyte antibodies (HLA) are routinely measured in patients awaiting transplant, with the results expressed as a percentage of reactivity. By convention, a patient with a panel reactive antibody (PRA) value of > 10% is considered sensitized. A comprehensive longitudinal analysis of the UNOS database showed that elevated PRA's were independently associated with impaired graft survival, even after a negative cross match transplant [13], and other studies have shown that increased PRA's correlated with impaired graft survival and coronary allograft vasculopathy [19,20]. The mechanism by which sensitization negatively impacts graft survival is likely multifactorial and includes an increased likelihood of a positive crossmatch, acute rejection, earlier development of coronary allograft vasculopathy, and longer waitlist times. Sensitization often occurs as a consequence of exposure to homograft tissue, blood products, or mechanical circulatory support [21]. While there are a small number of positive cross match transplants which have been completed, these show a higher incidence of rejection within the first post-transplant year [22]. Given the increasing number pediatric OHT recipients who previously had CHD, or were supported with a VAD, the population of sensitized patients has

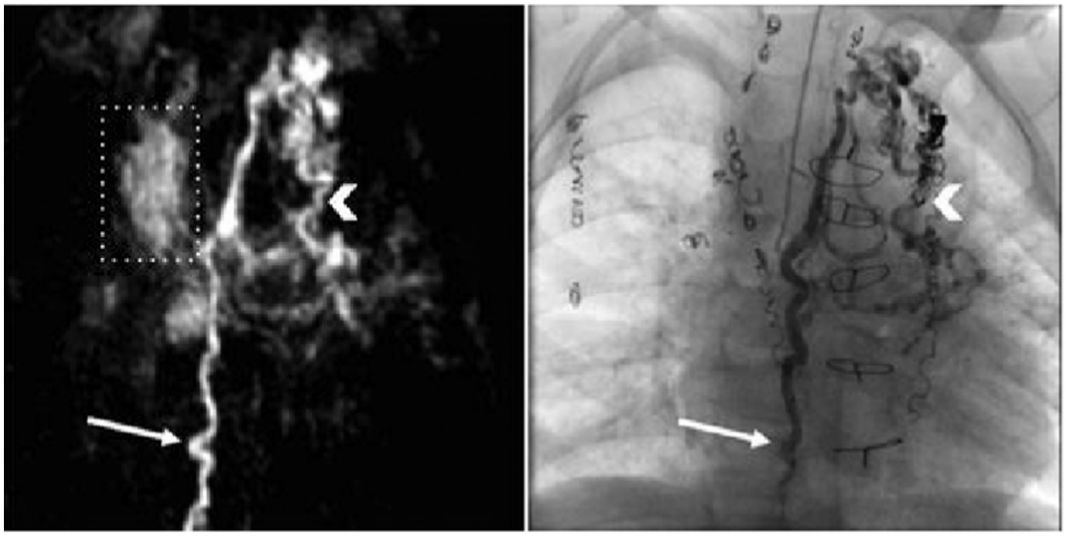

**Fig. 6.** DCMRL and Lymphagiogram of a patient with PB: Dynamic contrast enhanced magnetic resonance enhanced lymphangiogram and lymphangiogram show an abnormally dilated and tortuous thoracic duct with lymphatic flow towards the lungs.
Dori Y, et al. Circulation 2018.

increased, and will likely continue to do so, highlighting the need for increased attention to this cohort.

### 3.4. High risk social situations

Studies have shown that long term survival is worse in OHT recipients with lower socioeconomic status (SES) [23,24], that these patient have higher rates of rejection, hospitalization and infection, and that their adherence to immunosuppressive medications is decreased [25,26]. Inadequate social support and noncompliance with the medical regimen are considered contraindications for heart transplant (ISHTL listing guidelines 2016). These present some challenging but important questions with respect to suitability for transplant. It is a difficult situation to propose devoting a limited organ to a recipient without adequate social support or a history of noncompliance on multiple occasions, yet at the same time it is ethically disquieting to deny a child a life sustaining therapy due to reasons that for which the child was not responsible (Table 1).

## 4. Promising therapies

### 4.1. Therapies which improve transplant candidacy

Over the past two decades there has been a shift in the understanding of VADs from a salvage therapy to a mechanical form of cardiac rehabilitation which reestablishes normal cardiac output and end organ perfusion, and with that offers the opportunity for nutritional recovery and physical rehabilitation. Overall, patients supported with VADs prior to transplant do at least as well though as those bridged to transplant without mechanical circulatory support (MCS), and far better than those bridged with ECMO.

Placing a VAD in small child, or one with CHD, can be challenging due to both patient size and anatomy, particularly if an intracorporeal device is preferred. It can be difficult to place a device designed for an adult in a pediatric chest, and there is the risk of anatomic obstruction to the VAD inflow. This is clearly evident in the single ventricle population. Overall, those patients with CHD and a VAD have worse outcomes then their counterparts with cardiomyopathy [27].

However, novel surgical approaches have been developed, with atrial cannulation and sometimes excision of the atrioventricular (AV) valve which have allowed for the placement of VADs in some of these patients, with discharge to home and eventual successful transplant [28–30] (Fig. 4). Additionally, the Jarvik Infant 2015, which is an intracorporeal pediatric-specific continuous flow VAD is now being tested as part of a clinical trial, and offers the possibility of an FDA approved VAD specifically designed to meet the circulatory needs of infants and children with advanced heart failure [31,32] (Fig. 5). Given the role that VADs have in pre-transplant rehabilitation, increasing their availability for small children and those with CHD is an important step in improving the risk profile for this cohort, and making them better candidates for eventual transplant.

### 4.2. Therapies which avoid the need for transplant

As the process of single ventricle palliation has improved, there is an increasing number of children and young adults with failure of their Fontan circulation, often with relatively preserved ventricular function. Manifestation of Fontan circulatory failure, including the development of protein losing enteropathy (PLE) and plastic bronchitis (PB), can be severe and refractory to the available medical therapies, leading to listing for OHT [33–35]. However, in the past decade there have been an increasing awareness of the role that the lymphatic system plays in these pathologies, and with them the development of techniques to interrupt or redirect lymphatic flow (Fig. 6). In some instances, these interventions have had the effect of relieving patients' symptoms, and the possible need for transplant [36–39]. Given that pediatric donors are a limited and finite resource, therapies which restore a child's circulation to the point where they no longer need a transplant are incredibly important.

## 5. Conclusions

The population of pediatric patients with end stage heart failure is growing, and times on the transplant wait list are getting longer, increasing the imperative of prudent candidate selection. It is often difficult to predict who will thrive after transplant, but those with complex CHD, end organ dysfunction, and challenging social environments are at particular risk for adverse outcomes. While challenging, identification of those patients will allow for better patient selection, timely deployment of MCS, and an improved understanding as to whether the risks of death after transplant are so high as to preclude listing. Just as important as the recognition of high risk patients is the continued investment in improved heart failure therapies for those subgroups we know to be at high risk, either in the interest of improving transplant candidacy, or ideally, obviating the need for transplant entirely.

## Declaration of Competing Interest

Joseph Rossano: consultant for Amgen, Novartis, CSL Behring.
Jonathan Edelson: no disclosures or conflicts of interest.

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