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Pediatric cardiac transplantation

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ABSTRACT

Heart transplantation in pediatric patients generally arises as a treatment option of last resort, that is, the indication is for patients with heart failure of various etiologies, with potential or actual end-organ dysfunction, in whom there are no reasonable, long-term options for life-prolonging therapy. The concept of heart failure is complex in a pediatric population, particularly those with congenital heart disease. While heart failure may refer simply to systolic dysfunction leading to low cardiac output, it can also encompass: diastolic dysfunction in restrictive cardiomyopathy; single ventricle physiology without an option for stable palliation. A good candidate should have a predicted life expectancy less than the median lifetime of a transplanted heart. Significant improvement in survival has been observed over time with 1- and 5-year survival approximately 90% and 80% in the contemporary era.

Introduction

A half century ago there was a race to perform the first human heart transplant. Those involved included the visionaries Norman Shumway, Christiaan Barnard, and Adrian Kantrowitz. On December 3, 1967, Dr. Barnard and his team at Groote Schuur Hospital in Cape Town South Africa implanted a human heart into a 53-year old man, making world history.[1] What many today are unaware of is that 3 days after Dr. Barnard's accomplishment, Dr. Adrian Kantrowitz conducted the second human heart transplant, this time in the United States and on an infant with Ebstein's malformation of the tricuspid valve.[2] Pediatric cardiac transplantation since the late 1960's had been rare events until the 1980s. After the introduction of cyclosporine, the annual volume increased, reaching a plateau over 400 cases by the early 1990s as reported to the Registry of the International Society for Heart and Lung Transplantation (ISHLT).[3] Similar to the volume of cases per annum, significant improvement in survival has been observed over time with 1- and 5-year survival approximately 90% and 80% in the contemporary era.[4] Outcomes, however, are largely dependent upon a number of factors including the selection of appropriate candidates and management during the waitlist, operative, and postoperative time periods.

Heart transplantation in pediatric patients generally arises as a treatment option of last resort. That is, the indication is for patients with heart failure of various etiologies, with potential or actual end-organ dysfunction, in whom there are no reasonable, long-term options for life-prolonging therapy. The concept of heart failure is complex in a pediatric population, particularly those with congenital heart disease. While heart failure may refer simply to systolic dysfunction leading to low cardiac output, it can also encompass: diastolic dysfunction in restrictive cardiomyopathy; single ventricle physiology without an option for stable palliation, such as pulmonary atresia with intact ventricular septum and right ventricle-dependent sinusoids; failed single ventricle palliation as seen in protein losing enteropathy or plastic bronchitis post-Fontan; or intractable arrhythmia (Table 1).[5] A good candidate should have a predicted life expectancy less than the median lifetime of a transplanted heart. This concept is important to consider with current survival statistics, as an infant or child undergoing the procedure would likely need consideration for transplantation again in the late teen or early adult years. When a patient does reach this point, it is reasonable to perform a transplant evaluation to determine if the treatment is appropriate for the patient, and the patient appropriate for the treatment. Unfortunately, the imbalance between those in need of transplantation and the supply of donor organs remains high.

Initial referral and work-up

When referred for evaluation, the initial steps include determination of disease severity and whether there are any reversible or treatable factors responsible.[6] This is all highly dependent on the etiology of heart failure, which itself is variable by age group. In general, congenital heart disease accounts for approximately half of the cases of heart transplantation in patients 5 years old

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Table 1
Indications for pediatric heart transplantation.

Acceptance criteria (NYHA III/IV)[a]
Congenital heart disease
Coronary artery disease
Dilated/left ventricular noncompaction cardiomyopathy
Hypertrophic cardiomyopathy
Restrictive cardiomyopathy
Cardiac tumor
Posttransplant vasculopathy
Other[b]

[a] New York Heart Association III (symptoms of heart failure with minimal exertion) and IV (symptoms of heart failure at rest).
[b] Including unrepaired or failing palliated congenital heart disease, intractable arrhythmia; NYHA III/IV not necessary.

and younger, one-third of those aged 6–10, and less than one-quarter of the adolescent group. Cardiomyopathy as a cause shows essentially the opposite trend. Re-transplantation amounts to a small portion of recipients in all age categories, and serves as neither a benefit or detriment during evaluation.[4] If there are no alternative treatment options, then a complete evaluation is undertaken comprised of medical, surgical, and psychosocial evaluation. The first, and possibly most important step, in the process is to have an in-depth discussion with the family/caregivers, and patient if appropriate, to fully inform of the benefits, risks, and outcomes expected with heart transplantation. Only after they have provided their informed consent should the evaluation proceed.

For the pediatric and adolescent patient, the generally recommended medical testing is listed in Table 2.[7] Not all testing is appropriate or needed for a given patient, and requirements are center-dependent. However, adequate information to make a prediction about outcome after transplantation is necessary, and to determine whether any contraindications exist.

Laboratory testing

Specific laboratory testing in patients is indicated to identify end-organ dysfunction, active infections, historical infectious exposures, coagulopathy, neoplasm, blood type, nutritional deficiencies, effects of chronic medications, and sensitization to human leukocyte antigens (HLA) as represented by panel reactive antibodies (PRA). A proposed laboratory panel is presented in Table 2. Based on initial testing, diagnosis, or other comorbid conditions, further diagnostic studies, particularly imaging, may be indicated to assess end-organ function, vascular access, surgical approach, or presence of neoplasm.

Cardiac catheterization

The ISHLT recommends right heart catheterization should be performed on all adult candidates for listing, and periodically thereafter until transplantation. In cases of suspected myocarditis, biopsy can help determine the extent of involvement and potential for reversibility[8]; however, recent advances in cardiac magnetic resonance have led to less dependence on invasive studies.[9,10] The same may be said of determination of complex anatomy by computed tomography and cardiac magnetic resonance, but data regarding hemodynamics remain the unique purview of catheterization, especially when a potential intervention is discovered. Determination of PVR by catheterization, generally indexed to body surface area (PVRI), is of particular importance in pediatric patients given the potential impact on outcomes after transplantation.[11]

Table 2
Recommended testing for pediatric heart transplant evaluation.

Phase	Testing/evaluation
Diagnostic	Cardiac catheterization – Assess PVRI and reactivity if indicated, anatomy
	Cardiopulmonary exercise testing[a] – Obtain VO_2 or other center-specific testing
	Imaging – Echocardiography, computed tomography,[a] cardiac magnetic resonance[a] to determine cardiac anatomy and/or surgical approach
Blood Work	Chemistry – Comprehensive metabolic profile – Liver function tests – Thyroid function tests
	Hematology/immunology – HLA typing – Panel reactive antibody – Blood type (confirmed ×2) – Complete blood count – Immunoglobulin levels[a]
	Infectious – CMV, EBV, hepatitis A/B/C active/historical status – HIV – Tuberculosis (purified protein derivative or QuantiFERON-TB) – Herpes – Varicella – Toxoplasmosis
Psychosocial	Behavioral/psychiatric assessment of patient[a] Social work assessment of family/home environment Assessment of prior medical compliance Palliative Care Team[a]
Financial	Insurance and resource availability
Other[a]	Pulmonary function testing Ultrasound assessment of liver and kidneys Ultrasound assessment of vascular access Medical/surgical consultation as indicated by patient history Genetic testing Neuropsychological testing

CMV = cytomegalovirus; EBV = Epstein–Barr virus; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; PVRI = indexed pulmonary vascular resistance; VO_2 = peak oxygen uptake.
[a] Testing performed if indicated and appropriate, may be center-dependent.

Cardiopulmonary exercise testing

The inclusion of cardiopulmonary exercise testing (CPET) in evaluation for transplantation in pediatric and adolescent patients is variable. For those in whom CPET can be performed, assessment of peak oxygen consumption (VO_2) may be useful in the decision to list for transplantation. Guidelines from ISHLT use VO_2 cut-off values of < 14 ml/kg/min or $\leq 50\%$ predicted as guides to consider listing for adult patients, but offer no specific guidance on pediatric patients.[12] In some cases, pediatric patients are incapable of participation in CPET due to developmental status or disability. Pulmonary and musculoskeletal disease can also negatively affect results. Moreover, normal values for pediatric patients are different than in adults,[13] and patients with palliated single ventricle physiology may have a depressed baseline.[14] One recent single center study suggests that $VO_2 \leq 50\%$ predicted was associated with outcomes in children with biventricular circulation, but not those with palliated single ventricle physiology.[15] Other parameters, such as heart rate reserve, minute ventilation/carbon