

Pediatric heart transplantation – indication and preoperative assessment

Iolanda Muntean¹, Asmaa Carla Barmou², Daniela Toma²

¹University of Medicine, Pharmacy, Science and Technology “George Emil Palade”,
Tg. Mures, Romania

²Clinic of Pediatric Cardiology, Emergency Institute of Cardiovascular Diseases and Transplantation,
Tg. Mures, Romania

ABSTRACT

Pediatric heart transplantation is now considered a standard therapeutic care for infants and children with end stage heart disease. The indication for heart transplantation depends on the etiology of heart failure, and therefore is related to the age of the children: congenital heart defects predominate in infants and cardiomyopathies in older children. Because of the evolvement in surgical strategy of the congenital heart defects, the indication for heart transplantation is in continuous upgrading. The waiting list is stratified according to the patient status. This review focuses on the indications for pediatric heart transplantation. Also, because of the need of a rigorous assessment of the potential recipients, we present a check-list for the pretransplantation assessment of the receptor.

Keywords: heart transplantation, indication, pediatric, cardiomyopathies, congenital heart defects

INTRODUCTION

Pediatric heart transplantation is now considered a standard therapeutic care for infants and children with end stage heart disease of various etiologies, particularly those with cardiomyopathies and congenital heart disease (CHD).

The first pediatric heart transplantation was conducted in 1967 in New York, but the patient had died after 6 hours. Over time, significant improvement of this treatment option has been observed due to advancement of surgical techniques and anti-rejection therapies such as the introduction of calcineurin inhibitors (1). The Registry of the International Society for Heart and Lung Transplantation (ISHLT) collected data from 177 heart-lung transplant centers and reported over 12.000 heart transplant in children. Improvement in survival was recorded over time with 80-90% survival at 1 and 5 years post-transplant. However, survival rates depend upon numerous factors such as a correct management before and after transplant and a rigorous selection of the candidates (2).

Despite the advancement of supportive cardiovascular therapies, new-born and infants below 6 months awaiting heart transplant have the highest waitlist mortality among all children, with a percentage of almost 23% (3).

Heart transplantation is the recommended therapeutic strategy in infants and children with end-stage heart failure (HF) refractory to maximal medical treatment or associated with malignant arrhythmias, restrictive cardiomyopathy, severe limitation of physical activity or growth failure. Ryan T et al. consider that heart transplantation is an option of last resort and in order for a patient to get access to the waiting list, he must have a life expectancy less than the life expectancy of a transplanted heart (2).

Guidelines for management of HF in children proposed different classifications and grading systems for HF such as Ross classification and New York Heart Association (NYHA) classification (4,5). In order to emphasize the progression of HF, it has been described an additional grading system, with 4 stages (A-D). Stage A includes patients at risk to develop HF

Corresponding author:

Asmaa Carla Barmou, MD

E-mail: asmaa.carla@yahoo.com

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in the future, such as patients with CHD, family history of cardiomyopathy or exposed to cardiotoxic medication. Stage B includes patients with structural or function abnormalities without symptoms of HF. Stage C includes patients from stage B with characteristic symptoms of HF. Stage D is the end stage of HF and includes patients who require continuous therapy with inotropic agents or prostaglandin in order to maintain the patency of ductus arteriosus, mechanical ventilatory support and/or circulatory support (6).

In order to complete the waiting list for transplantation, Renlund et al. elaborated the United Network for Organ Sharing (UNOS) pediatric listing stratification. According to this, children with stage D heart failure are listed as UNOS status 1 candidates (1A or 1B), while those with stage C heart failure are listed as UNOS status 2 candidates (7).

The indication for heart transplant in pediatric population depends on the etiology of heart failure, therefore is related to the age of the children: infants <1 year old who need heart transplant have CHD, whereas most of older children suffer from cardiomyopathies (8).

CARDIOMYOPATHIES

Approximately 75% of children and adolescents above 10 year old that require heart transplant have primary muscle disease or cardiomyopathies whereas in the age group <10 years, cardiomyopathies are accounted for only 45% of cases (9). Based on multicenter observational studies, recent guidelines consider Class I indication for heart transplantation cardiomyopathies associated with stage D (UNOS status 1) and stage C (UNOS status 2) of HF (4). Associated sudden death or untreatable life-threatening arrhythmias represent also a class I indication (4).

From cardiomyopathies subtypes, dilated cardiomyopathy (DCM) is the most common indication for heart transplant in pediatric population (51% of cases), followed by restrictive (RCM) and hypertrophic cardiomyopathies (HCM). In DCM, identification of etiology is important, because the underlying disorders per se (metabolic or neuromuscular) may have lower survival rate than the DCM without transplantation (10). Risk factors for transplantation or death in DCM are age greater than 6 years, HF signs at presentation and lower LV systolic function (11). Risk factors for death on the waitlist include older age at diagnosis and use of ventilator (12).

In HCM, the identified risk factors for transplantation or death include: younger age (< 1 year), low weight and LV ejection fraction, higher wall thickness at the moment of diagnosis (10,13). Also, the risk fac-

tors for waitlist mortality are: UNOS status 1 or younger age (14).

Regarding RCM, even though is rarer in children compared with HCM, transplantation for this category of patients is more frequent due to a poor long-term prognosis, with a survival rate at ten years after the diagnosis of almost 20% (15). Risk factors for waitlist mortality are: UNOS status 1, younger age, use of ventilator, ECMO, need of inotrope or ventricular assist devices (16). Heart transplantation is a class I indication in pediatric restrictive cardiomyopathy with stage C of HF and reactive pulmonary hypertension.

CONGENITAL HEART DISEASE

Data collected from ISHLT during 2000-2012 shows that almost 55% of infants younger than 1 year old with end-stage HF that underwent a heart transplant were diagnosed with CHD (17). Among this category of patients, the most common pathology is single ventricle lesions (36%) (18).

During the 90s, the most frequent indication for heart transplant in infants was hypoplastic left heart syndrome. Due to significant progress registered to palliative surgical techniques such as Norwood palliation or hybrid procedures, and the limited number of pediatric donors, according to the guidelines, heart transplantation is not indicated as standard therapy for any CHD (class III) (4). However, infants diagnosed with single ventricle associated with certain conditions such as severe ventricular dysfunction, severe stenosis/atresia of coronary arteries (proximal), or atrioventricular or semilunar valvular regurgitation/stenosis are listed for heart transplantation (class IIA indication) (4,21).

Nowadays, as most of infants undergo corrective or palliative surgery and survival rates of infants with CHD improves, therefore the number of children above 1 year with corrected or palliated CHD that require cardiac transplant increases. Those with associated stage D or C of HF present class I indication (4). However, these patients can be listed for heart transplantation even in the absence of severe systemic ventricular dysfunction if there is associated one of the following: fixed, irreversible PHT, severe aortic or atrioventricular insufficiency, severe cyanosis or persistent protein-losing enteropathy, hepatic cirrhosis or pulmonary arterio-venous collaterals(class IIA indication) (4,19-21). Also, the presence of plastic bronchitis in Fontan patients is an indication for heart transplantation, due to the risk of life-threatening events, with potential of resolution of this after heart transplantation (10,21).

In the “failed Fontan“ patients the following are considered risk factors for death after listing for heart transplantation: less than 6 months from the Fontan procedure, UNOS status 1 and ventilator support (22).

PRE-TRANSPLANTATION ASSESSMENT

Because of the small number of pediatric heart donors, major efforts are ongoing to develop accepted indications for pediatric heart transplant. Significant limitations still exist because international guidelines are based on small studies or expert opinions due to lack of randomized studies. Furthermore, there are still controversial issues between clinicians related to patient selection and listing for transplant. Therefore, a complex perioperative selection should be performed in order to avoid judgment errors such as listing a patient with reversible HF or with irreversible pulmonary hypertension. The experience gathered in our transplant center was used to make a complete perioperative checklist in order to improve patient selection before listing for heart transplant, as it is seen in figures 1A and 1B.

All potential recipients should complete a complex pre-transplant evaluation. The first step in this process is to educate and prepare patients and their families about the complex post-transplant care, the benefits, outcomes and medical follow-up. The key aspect of psychosocial assessment is to determine the level of support and to increase awareness of this complex procedure because lack of adherence to medical treatment was associated with medication errors, acute rejection, infections or even death (1). Also, the neurological status of the patients should be evaluated. The efficacy of heart transplantation is questionable in children with poor family support, noncompliance or neurological/behavioral disorders (relative contraindication).

After the psychosocial examination, the recipient should undergo a rigorous selection criterion because pre-transplantation screening with a full evaluation of the underlying heart failure etiology and comorbidities of the recipient is mandatory for a successful cardiac transplantation.

First of all, a full medical history that includes previous medical records, prior surgical interventions

CHECKLIST FOR HEART TRANSPLANTATION

Date: _____

FIRST NAME _____ SURNAME _____

DATE OF BIRTH _____ AGE _____

ADDRESS: Country _____ City _____

Street _____ Number _____ Apartment _____

PHONE _____

BLOOD TYPE _____

DIAGNOSIS: _____

PRE-TRANSPLANT HISTORY:

Social History and environmental risks:

- Name of the children's father _____
- Cohesion of family: _____
- Living situation and conditions (number of persons in the house, number of bathrooms)

Complete family history:

Past medical history:

- Complete immunization history
- Known allergies
- Childhood diseases
- Major medical or surgical diseases
- History of infections

History of present disease:

- Chronological history of the disease
- Description of signs and symptoms
- Past and current medication

PRE-TRANSPLANT BASELINE EVALUATION:

- Complete clinical exam
- Child's weight/height - body mass index
- Heart failure stabilization (NOVA/IOSS and AMA)

1A

NEUROPSYCHIATRIC EXAM

- Psychosocial assessment
- Psychiatric disorders
- Substance use history (drugs, smoking, alcohol)

LABORATORY SCREENING

- Complete blood count
- Coagulation profile (partial thromboplastin / PTT)
- Arterial blood gas analysis
- Serum electrolyte panel (sodium, potassium, magnesium, calcium, for lead assessment)
- Protein panel (total protein and albumin)
- Liver function panel (TRANSAMINASES: Alanine Aminotransferase-ALT and Aspartate Aminotransferase-AST, bilirubin)
- Renal function panel (Serum creatinine level, creatinine clearance, blood urea)
- Lipid profile (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides)
- Acute phase reactants (CRP, C-reactive protein, ESR, erythrocyte sedimentation rate)
- Blood glucose measurement
- Urine urine culture
- Infectious disease testing (Viral serology)
 - Hepatitis B- HBs antigen assay, Anti-HBs assay, Nucleic Acid testing
 - Hepatitis C- Anti-HCV assay, Nucleic Acid testing
 - Human immunodeficiency virus: Anti-HIV antibodies, Nucleic Acid testing
 - Cytomegalovirus: Anti-CMV antibodies IgM, IgG
 - Epstein Barr Virus- Anti-EBV antibodies IgM, IgG
 - Syphilis: Venereal Disease Research Laboratory / VDRL test, Rapid Plasma Reagin - RPR test
 - Toxoplasma: Anti-Toxoplasma antibodies
- Donor compatibility testing - Blood group and Rh typing, Panel reactive antibody

CARDIAC EVALUATION

- Blood pressure measurement
- Electrocardiogram
- Echocardiography
- Chest radiography
- Right heart catheterization

ABDOMINAL ULTRASOUND

1B

FIGURES 1A, 1B. Checklist for heart transplantation

and a history of previous vaccinations should be taken.

Second step prior to transplant is to determine specific laboratory panel in order to identify end organ dysfunctions and comorbidities. Uncontrolled end-organ dysfunctions such as renal or hepatic diseases that are expected to shorten life expectancy are one of the main contraindications of both adult and pediatric heart transplant (8). Due to the fact that end organ damage may be related with the heart disease and a low cardiac output, some consider liver or renal failure to be relative contraindication to heart transplant and may be reversible. But because immunosuppression drugs can be hepatotoxic or nephrotoxic, this part is debatable due to an increase risk of mortality post-transplant (23). In case of associated end organ dysfunction, multiorgan transplantation may be considered (4).

Also, pre-transplant laboratory screening should include specific testing for bacterial, viral, fungal and parasitic infections. Active infection should be treated before transplant in order to minimize the chances of infectious complications after transplant due to severe immunosuppression. Viral infections with some etiologies that have an increased potential of reactivation such as Epstein-Barr virus (EBV) or cytomegalovirus (CMV) are not listed as contraindications for heart transplant, but patients should be permanently monitored in order to determine the current status (2). Chronic viral infection such as HIV and hepatitis (B or C) was considered long time an absolute contraindication, but due to successful antiretroviral therapy, successful cardiac transplant in this category of patients have been performed (24). Still, this issue remains controversial and many transplant centers consider chronic viral infection a contraindication for heart transplant.

Prior to transplant, is necessary to include measurements of anti-human leukocyte antibodies (HLA) in order to determine rejection risk and with donor HLA is compatible. HLA sensitization is determined by panel reactive antibody (PRA), a value above 10% of the PRA is considered to be sensitized. Studies have shown that a sensitive PRA with elevated values is associated with post-transplant complications such as graft rejection and coronary allograft vasculopathy, with a negative effect on long term prognosis (25).

Previous surgical interventions in CHD patients, human homograft materials and blood product transfusion can increase the risk of allosensitization, with a worse outcome (21). Auerbach et al. demonstrated better results (increased graft survival, decreased rejection rate) in univentricular heart patients without prior surgical interventions (26).

After the laboratory panel, further diagnostic studies such as imaging investigations-echocardiography and computer tomography (CT) are indicated in order to assess surgical approach and cardiac and vascular anatomy. Echocardiography is a valuable tool in order to collect data regarding heart function. CT or magnetic resonance are mandatory for assessment of some anatomic factors such as pulmonary vein stenosis and pulmonary artery hypoplasia that are considered to be contraindications for cardiac transplant due to an increased posttransplant morbidity and mortality (23). Also, the aortopulmonary collaterals developed in Fontan circulation can preclude the graft function. Identifying them with imaging investigations and coil embolisation may be useful (21).

Most centers consider active neoplasm and ongoing chemotherapy as a contraindication for heart transplant. However, in context of oncologic diseases, some centers consider that listing for heart transplant should be individualized based on the type of malignancy and the risk of recurrence of the tumor. Some centers consider that one must be in remission for at least 2 years before transplantation (27).

Associated comorbidities like diabetes mellitus, or obesity may increase the risk of hypertension, infections, dyslipidemia and consequently may influence transplant coronary arteriopathy (4).

ISHLT guidelines recommend right cardiac catheterization in order to assess vascular access, to collect data regarding hemodynamics and to determine pulmonary vascular resistance (PVR) indexed to body surface area (2). Currently, $PVR > 6$ Wood units(WU)/ m^2 without response to pulmonary vasodilators and a transpulmonary gradient > 15 mmHg are considered cut-off values for heart transplant listing by many centers due to the risk of right ventricular dysfunction post-transplant (28). But recent studies have shown that a selective adult and pediatric population, with $PVR > 9$ WU/ m^2 with responsive vasodilator testing with pulmonary vasodilators, underwent successful transplantation with a survival rate of almost 78% at 30 days after transplant (29). Therefore, if PVR is above 6 WU/ m^2 , vasodilator testing should be performed, and if vascular resistance drops below 6 WU/ m^2 , cardiac transplant could be considered. Some authors consider that the reversibility of PVR is more important than the value itself (21). However, PVR index > 6 WU/ m^2 has been identified as important risk factor for death. Other factors are: decreased renal function (Cl creatinine < 40 ml/min), seropositivity for hepatitis type C, PRA $> 40\%$ and age < 1 year (21,30).

CONCLUSIONS

Heart transplantation is the recommended therapeutic strategy in infants and children with end-stage heart failure. The indication for heart transplant in pediatric population depends on the etiology of heart failure, and therefore is related to the age of the chil-

dren: CHD predominate in infants and cardiomyopathies in older children. The waiting list for heart transplantation is stratified according to the patient status (1A, 1B, 2). Due to a limited number of pediatric donors, a rigorous assessment of potential recipients should be made.

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