Chapter

Pediatric Heart Transplantation

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Abstract

Despite advances in medical management, patients submitted for heart transplantation procedures still are at risk to development of complications. This chapter will discuss some specific topics of pediatric heart transplantation, focusing on perioperative care: (i) recipient management, (ii) donor evaluation, (iii) immunosuppression, (iv) early postoperative management, (v) complications, and (vi) conclusions.

Keywords: heart transplantation, child, complications, immunosuppression, management, perioperative period, heart failure, mechanical circulatory support, pediatric

1. Introduction

Heart transplantation (HT) has been the therapeutic option for patients with complex congenital heart disease and cardiomyopathies with heart failure (HF) refractory to conventional treatment [1–4].

Despite advances in molecular biology, immunosuppressive drug therapy, the knowledge of the potential complications that may occur after the procedure are essential to improve the quality of life of patients and their survival.

In this chapter we will discuss:

1. Recipient management
2. Donor evaluation
3. Immunosuppression
4. Early postoperative management
5. Complications
6. Conclusions

2. Recipient management

The main types of pediatric heart diseases considered for heart transplantation are [1]:

- cardiomyopathies with refractory heart failure (**Figures 1** and **2**);
- congenital heart diseases with or without ventricular dysfunction and/or in natural history evolution that do not present the possibility of a new therapeutic intervention;
- patients undergoing heart transplantation due to graft vascular disease, rejection and/or graft failure.

The clinical manifestations of heart failure in children vary according to age of the patient and severity of disease. In infants, the most common signs and symptoms are poor weight gain, tachypnea and diaphoresis during feeding and fatigability. Young children may present abdominal pain, vomiting, nausea, poor appetite, fatigability,

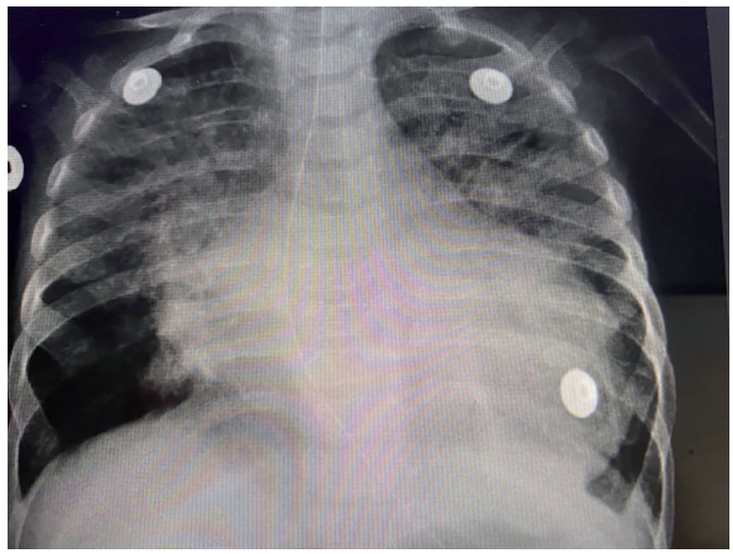

Figure 1.
Chest X-ray showing enlargement cardiac área in a child with dilated cardiomyopathy.

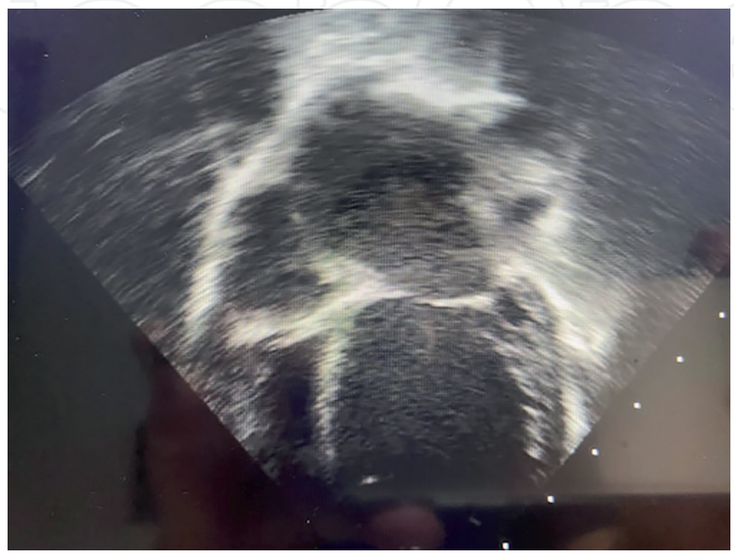

Figure 2.
Echocardiogram showing enlargement of left ventricle chamber in a child with dilated cardiomyopathy.

Clinical status
Pulmonary hypertension
Frailty
Pre-transplant vaccination/immunization
Mechanical assist device
Multidisciplinary approach

Table 1.
Specific topics for evaluation.

recurrent cough and failure to thrive. In adolescents, abdominal pain, anorexia, exercise intolerance, dyspnea, oedema or syncope may be found. Nowadays, heart failure in children can be classified and categorize of the stage and severity by the modified NYHA, stages of heart failure infants and children and recommended therapy (stage A, B, C and D), modified Ross classification and by INTERMACS, which can help in decision making. The INTERMACS classification was initially developed to consider the patient for mechanical circulatory support [5–8]. Pediatric patients with stage D heart failure are listed for heart transplantation [1, 6].

There are some important topics [1] to be addressed at the moment to evaluate a pediatric recipient for heart transplantation (**Table 1**):

1. The clinical status of patient: if the patient is in the intensive care unit receiving drugs with continuous infusions such as phosphodiesterase 3 (PDE3) inhibitors (milrinone) or epinephrine and anti-congestive medications; if the patient is with ventricular assist device or if the patient is at outpatient clinics.

   The clinical status will determine if the patient is in priority or not for heart transplantation when listed;

2. The type of anti-congestive medications for heart failure: diuretics, drugs that reduce afterload (angiotensin-converting enzyme inhibitors), ivabradine, sacubitril/valsartan and beta-blockers (metoprolol succinate and carvedilol) for improvement of symptoms and reduction of cardiac work;

3. Pulmonary vascular resistance index (PVRI): children who are candidates for heart transplantation and who present a high pulmonary vascular resistance index should be considered for the use of pulmonary vasodilators inhaled and intravenous (nitric oxide, prostacyclins, nitroprusside and milrinone). Prolonged use of inotropic agents may reduce pulmonary resistance to pulmonary vascular resistance índex < 6 Woods units/m^2 or transpulmonary gradient < 15 mmHg. Patients with pulmonary hypertension are refractory to medical therapy can be a candidate for mechanical assist devices to try to reduce the PVRI;

4. Nutritional assessment and support must be performed so that the patient can be adequately prepared for the surgical procedure and its recovery. Moderate to severe wasting and elevated weight/height are considered a risk for mortality during the waitlist. The restriction of fluids and sodium is part of the recommendations in the treatment of HF.

5. Physical rehabilitation: a physical rehabilitation regimen should also be part of the treatment;

6. Anticoagulation: children with severe ventricular dysfunction are at risk of thrombus formation therefore anticoagulation or anti-platelet aggregation should be considered if the patient has previous history of thrombus.

7. Immunizations: immunizations must be carried out according to the vaccination schedule.

8. Frailty is one of the major concerns due to chronic heart failure and is considered a prognostic factor of morbidity and mortality;

- Pre-transplant specific assessments are in **Table 1**. They are performed according to the patient's history and clinical conditions.

- Laboratory tests for initial evaluation for heart transplantation are in **Table 2**. HLA antibody level greater than 70% is considered high and may compromise short- and medium-term survival outcomes after transplantation.

- The assessment of the multidisciplinary team is fundamental for the success of long-term follow-up. The multidisciplinary team including nurse, psychologist, social worker, physiotherapist, dentist and nutritionist provides information about the patient as well as the family's suitability for the transplant procedure. Psychosocial support is vital when the child becomes a candidate for heart transplantation, as there is a need to restructure the family routine as a result of outpatient follow-up.

Mechanical circulatory support has been an option for children with refractory heart failure.

ECMO in children should be considered to provide adequate systemic perfusion and oxygenation for myocardial recovery after cardiopulmonary bypass or in patients as a bridge for heart transplantation and considered for long-term mechanical circulatory support (MCS). The use of ventricular assist device (VAD) has been increased for bridge to heart transplantation, decision or destination. The type of VAD depends on the weight, body superface área and pulmonary hypertension. In general, infants

Chest radiology
Electrocardiogram
Echocardiogram
VO_2 measurement
Magnetic cardiac resonance
Endomyocardial biopsy
Cardiac catheterization
Angiotomography

Table 2.
Pre-transplant specific cardiac assessment.

Complete blood count
Biochemistry
Liver and kidney profile
Lipid profile
Albumin and total proteins
BNP and pro-BNP
PCR
Urine I
Parasitological examination of faeces
Serology for infections such as hepatitis, HIV, toxoplasmosis, Epstein-Barr virus, Chagas disease, PCR for CMV and EBV
Blood typing
Panel reactive antibody percentage: magnitude of sensitization of the pre-transplant patient (immune panel) with HLA typing

Table 3.
Laboratory tests for initial evaluation of heart transplantation.

are candidates for paracorporeal MCS and adolescents for implanted ones. The prevalence of children waiting for heart transplantation with MCS has been increased in the last years (**Table 3**).

3. Donor assessment

The potential donor must be evaluated in relation to the recipient. The topics for donor evaluation in children are in **Table 4**. Pre-existing cardiac anomalies such as coronary artery disease, valve anomalies, left ventricular hypertrophy, donor cardiac function, donor-recipient size matching should be addressed before accepting the potential donor.

Blood type
Weight and height
Determination of cause of death
Ischemic time
Age
Past medical history
Electrocardiogram
Chest X-ray
Echocardiogram
Serology for infections such as hepatitis, HIV, toxoplasmosis, Epstein-Barr virus, Chagas disease, PCR for CMV and EBV

Table 4.
Donor evaluation.

Recently, ISHLT Pediatric Consensus (DOAM) describes the principal recommendations for acceptance of the pediatric donor [9].

Donation after Circulatory Death (DCD) should be performed in centres with experience in marginal donor hearts, perioperative mechanical support, the use of ex-situ organ perfusion devices for preservation and transportation.

ABO-incompatible heart transplant procedure has been performed in children in some centres with results similar to ABO compatible due to the scarcity of donors.

4. Immunosuppression

Immunosuppression regimens are generally defined according to the period of transplantation and the presence of rejection [10, 11]:

- Induction
- Maintenance
- Rejection treatment

Induction therapy can be defined as prophylactic immunosuppressive therapy in the perioperative period, usually with cytolytic agents, to reduce the incidence of early rejection (**Table 5**). Nowadays, the use of induction therapy has increased and is not associated with an increase in infection and malignancy [12].

Different classes of drugs are used for initial and maintenance immunosuppression in children.

The most used initial regimens are composed of the association of corticosteroids, calcineurin inhibitors and antiproliferative agents (**Table 5**).

The use of tacrolimus as a calcineurin inhibitor and the replacement of Azathioprine as an antiproliferative agent with mycophenolate is the current trend in most centres worldwide.

Induction therapy
Thymoglobulin rabbit
Maintenance regimen
1. Calcineurin inhibitors a) Tacrolimus b) Cyclosporin
2. Antiproliferative regimen: a) Mychophenolate b) Azathioprine
3. Corticosteroids
4. Proliferation signal inhibitors a) Sirolimus b) Everolimus

Table 5.
Most common immunosuppression drugs.

EKG
Systemic blood pressure
Central venous pressure
Pulmonary artery wedge pressure
Arterial oxygen saturation
Mixed venous saturation
Urinary output
Lactate
Vital signs (temperature, heart rate, respiratory rate)

Table 6.
Monitoring in Early post-operative care.

Proliferation signal inhibitors (everolimus and sirolimus) are used in renal failure, graft vascular disease and lymphoproliferative disease in combination with a calcineurin inhibitor or in monotherapy (**Table 5**).

In children, it is important to address the avoidance of steroids as maintenance drug therapy due to failure to adequate height development.

5. Perioperative management

Perioperative management consists of some topics that are listed in **Table 6** [11–16].

6. Complications

In perioperative period, the main complications of transplantation can be inherent to transplantation, such as early graft dysfunction, right ventricular dysfunction,

Tricuspid valve regurgitation
Pericardial effusion
Vasoactive drugs
Vasoplegia
Right ventricular dysfunction
Pulmonary hypertension
Mechanical circulatory support
Early allograft dysfunction
Arrhythmias
Renal function
Hyperglicemia
Antibiotics prophylaxis
Fontan-patients management

Table 7.
Topics of perioperative care.

Clinical findings
Chest X-ray
EKG
Echocardiogram
Endomyocardial biopsy
Biomarkers

Table 8.
Methods for rejection diagnosis.

hyperacute rejection as well as due to the immunosuppressive medication itself: infection, systemic arterial hypertension and renal failure (**Tables 7** and **8**). In the late postoperative period, coronary allograft vasculopathy, tumour, primary graft dysfunction are some causes of long-term complications.

Rejection has been reported as the main cause of death after transplantation. The diagnosis of rejection is made by a combination of clinical signs and symptoms, non-invasive tests and/or endomyocardial biopsy, using the International Society of Cardiac and Lung Transplantation (ISHLT) criteria [14]. Several noninvasive methods have been reported such as echocardiography, cardiac magnetic resonance, electrocardiogram, Gallium-67 as well as biomarkers of injury or immunoreactivity such as BNP, troponin and donor-specific antibodies (DSA) for rejection surveillance in pediatric heart transplantation. These non-invasive methods have been described as high degree of specificity and low sensitivity and are useful for identifying those without rejection episodes. Therefore, endomyocardial biopsy is still the gold standard for rejection although there are risks related to the procedure such as venous occlusion, radiation and perforation.

6.1 Rejection treatment

Treatment of rejection should be directed towards the underlying aetiology, as well as the severity of the condition based on clinical, laboratory and pathological findings.

6.2 Acute cellular rejection

- Mild and asymptomatic (1R)—does not require treatment due to the high rate of spontaneous resolution and the absence of association with reduced long-term survival and graft vascular disease.

- Moderate and severe cell rejection (ISHLT ≥ 2R) (**Figure 3**)—should be treated with enhanced immunosuppression. If a patient with signs of ventricular dysfunction and needs vasoactive drugs, methylprednisolone therapy and antithymocyte globulin association is recommended. MCS should be considered if there is hemodynamic instability.

6.3 Humoral rejection

It includes the same schemes used to treat cell rejection, with high doses of corticosteroids and lymphocytolytic agents. Additionally, intravenous immunoglobulin

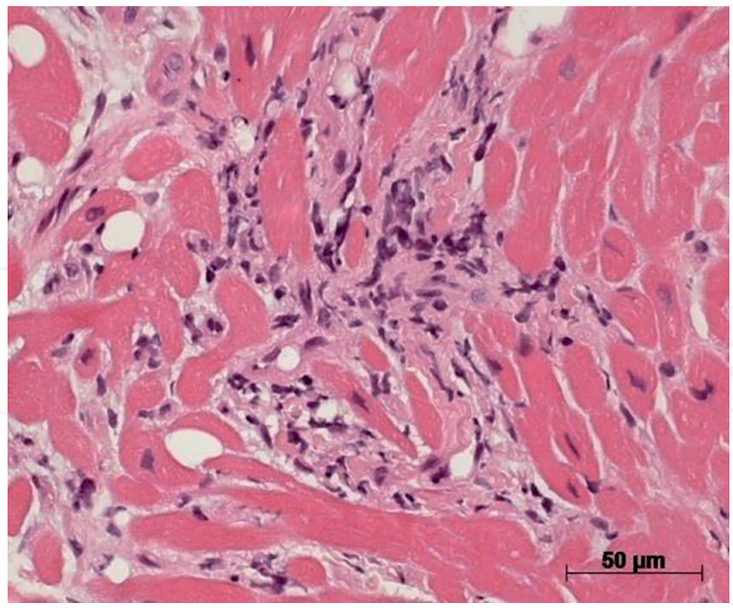

Figure 3.
Cellular rejection: a focus of inflammatory infiltrate with cellular aggression and architectural distortion in acute cellular rejection grade 2R.

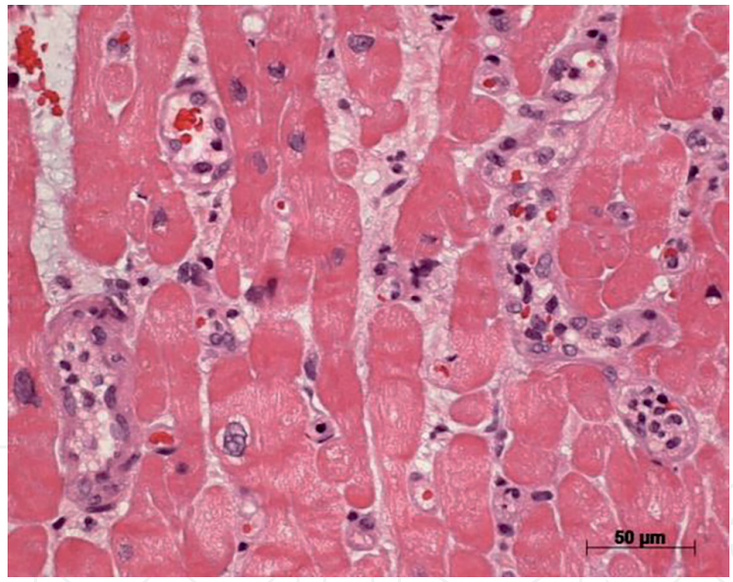

Figure 4.
Humoral rejection: interstitial edema and endothelial swelling of capillaries in antibody-mediated rejection. Note also the presence of mononuclear cells inside capillaries.

and plasmapheresis to remove circulating antibodies and specific therapies to target B cells (cyclophosphamide, mycophenolate and rituximab) can be used (**Figure 4**).

7. Conclusions

Heart transplantation is an option for refractory heart failure in children with cardiomyopathies and complex heart diseases. It is a highly complex clinical-surgical therapy that involves a specialized multidisciplinary team so that child care can be performed successfully. Nowadays, the Pediatric Heart Transplantation Society

(PHTS) has developed a database where clinical trials and robust research have been performed for the best care of this fragile pediatric population.

Acknowledgements

Dr. Luiz Benvenuti from the Pathology Department for the pictures of rejection.

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