44 Heart Transplantation

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TCH performed its first successful heart transplant in an 8-month-old child with dilated cardiomyopathy in November, 1984. Since that time, the heart transplant program has grown to be one of the largest and most successful programs of its kind in the world. In 2018, the program surpassed 400 transplants performed.

Indications and Contraindications

Heart transplantation becomes an option in any patient with end-stage heart disease (ESHD) that cannot be managed by other medical or surgical intervention. This includes any of the cardiomyopathies (dilated, hypertrophic, restrictive, or LV non-compaction) or CHD. Most patients with CHD have had prior surgical palliation, which has failed. Other patients are born with such complex CHD that there is no good surgical palliation available to them. Cardiac retransplantation may be indicated in patients whose primary grafts fail. The most common cause of graft failure is transplant-associated coronary vasculopathy.

At TCH, there are a few conditions that are considered absolute contraindications to cardiac transplant (Table 44-1).

Recipient Evaluation

Patients being considered for cardiac transplantation undergo a comprehensive evaluation process. That process begins with a detailed conversation with family members discussing evaluation, listing, the surgery itself, and postoperative follow-up. That discussion also includes the indications, risk and benefits of transplant as well as an expected lifestyle and prognosis for the patient. There is also a review of our institutional volumes and outcomes relative to other centers across the country.

The evaluation process includes an extensive panel of bloodwork designed to assess end-organ function in the patient, provide a roadmap of prior infection, and assess the patient's current immune status and human leukocyte antigen (HLA) sensitization. Imaging beyond standard CXR and echocardiograms may be required. Imaging is tailored to the individual needs of the patient but might include chest CT or MRI, as well as cardiac catheterization. A baseline ECG and Holter are required. In addition to transplant cardiology and CV surgery evaluations, the patient is seen by the transplant immunology and transplant infectious disease services. The patient is also seen by pharmacy, occupational and physical therapy, and nutrition. Consultation is required with our medical social worker, child life, and financial counselor. If possible, neuropsychological and developmental testing is also obtained. If this initial screening evaluation determines any additional concerns, additional consults may be obtained. Patients are commonly seen by the renal, neurology, and pulmonary services in order to complete their evaluation. Following acquisition of all of this information, a multidisciplinary medical review board meeting is held. Each consultant is asked

Table 44-1. Contraindications to cardiac transplantation.

Absolute contraindications	Comments
• Untreatable malignancy	
• Progressive and untreatable liver disease	
• Severe fixed elevated PVR	PVR >6 Woods units per m^2 measured in the cath lab, despite intervention with pulmonary vasodilator therapy
• Severe chronic obstructive pulmonary disease	
• Psychiatric disorder	Prevents a patient from adhering to or being able to comprehend their posttransplant care
• Hemodynamic compromise	MSOF such that the patient is unlikely to recover despite transplantation
Relative contraindications	**Comments**
• Active infection	
• Recent pulmonary infarction	
• HIV infection	
• Peripheral vascular disease	
• Chronic systemic illness with multiorgan involvement	
• History of noncompliance	
• Absence of a responsible caretaker	
• Current drug and/or alcohol addiction	Patient or parent caretaker
• Absence of resources to support transplantation and posttransplant follow-up	Including medications, living expenses and/or proper maintenance of a transplant environment, transportation, and medical care
• BMI >35 kg/m^2	
• Severe neurologic impairment	
• Pregnancy	

BMI: body mass index, MSOF: multi-systemic organ failure

to present their findings to the group at large and, finally, a vote for the candidacy of transplantation is obtained.

Listing Status

The United Network of Organ Sharing (UNOS) maintains the listing status for all patients (pediatric and adult) awaiting all solid organ transplantation. Their protected website is accessed through the internet. Potential pediatric donor heart recipients are actively listed into 1 of 3 separate categories:

- **Status 1A.** The highest priority category is status 1A. Patients meet criteria for status 1A listing if 1) they require continuous mechanical ventilation; 2) they require assistance with an intra-aortic balloon pump; 3) they have a ductal-dependent systemic or pulmonary circulation with ductal patency maintained by stent or prostaglandin infusion; or 4) they have hemodynamically significant CHD and require infusion of multiple IV inotropes or high doses of a single IV inotrope. Any patient that requires the assistance of mechanical circulatory support, either temporary or durable, meets 1A listing status.
- **Status 1B.** Patients qualify for 1B status if they require infusion of one or more inotropic agents but do not qualify for pediatric 1A status, or if a patient is <1 year of age at the time of initial registration and has the diagnosis of hypertrophic or restrictive cardiomyopathy.
- **Status 2.** All patients that are actively listed but do not meet status 1A or status 1B criteria are then listed status 2.

Patients are eligible for ABO incompatible heart offers if they are <2 years of age and their isohemagglutinin titers are ≤1:16. When a patient is eligible to receive a potential donor offer, our center is contacted to review the donor offer and determine if the donor offer is medically and surgically acceptable. Our center remains open 24/7 to receive donor offers.

Donor Evaluation

The donor evaluation process begins with a thorough review of the donor medical history. In particular, the cause of death and the presence or absence of downtime/CPR are important. Infectious history, malignancy, social history, and high-risk behaviors are important too. However, this crucial information is often unclear. Objective data (e.g., echocardiography, inotrope use, serum sodium, troponins) are also critical. The final decision regarding organ suitability is made by the procuring surgeon under direct vision. Typically, the recipient surgery starts only after the final decision has been made.

Surgical Technique

At TCH, we prefer to utilize the "bicaval" technique, in which the systemic venous return is reconstructed at the level of the caval veins (i.e., SVC and IVC). This is superior to the classic "biatrial" technique where the donor and native right atria are sewn together, as it preserves tricuspid valvar competency as well as electrical conduction. The downside includes the possibility of anastomotic stenosis, particularly at the SVC in small recipients. In patients with complex CHD, significant technical challenges exist, which may require modifications to the standard technique. One example is the

Table 44-2. Anesthetic and perioperative considerations following heart transplantation.

	Mechanism	Consideration	Treatment
Early considerations			
Sinoatrial dysfunction	Disruption of sinoatrial node	Severe bradyarrthmias	Temporary pacing, alpha 1-agonist (e.g., isoproterenol or epinephrine)
Ventricular dysfunction	Ischemia-reperfusion injury Recipient pulmonary hypertension Suboptimal organ preservation	Diastolic dysfunction RV dysfunction	Inodilators (milrinone) Epinephrine Optimize ventilation with 100% FiO_2 iNO Temporary VAD or ECMO
Late considerations			
Denervation of the donor heart	Disruption of baroreceptor reflex	Minimal HR response to: - Hypovolemia - Orthostatic changes - Anticholinergics	Use of direct agonist phenilephrine to increase SVR Epinephrine to increase CO and HR
Graft dysfunction	Chronic rejection	Ventricular dysfunction	Inotropic need Temporary VAD
Coronary artery vasculopathy		Coronary perfusion-pressure dependent	Maintain CPP Phenylephrine Correct anemia if present Temporary VAD

CO: cardiac output, CPP: coronary perfusion pressure, HR: heart rate.

presence of bilateral Glenn anastomoses; in select situations, the left Glenn is left in place, while the right Glenn is taken down for reconstruction with the donor right SVC.

Anesthetic and CPB Management

The conduct of anesthesia varies depending on the etiology of heart failure (CHD vs. no CHD) and/or the need for pretransplant VAD support. Patients on VAD support are usually physiologically more stable and tolerate better the induction of anesthesia. All repeat-sternotomy patients (e.g., palliated CHD and VADs) have a longer intraoperative course due to increased surgical complexity and a higher risk of postoperative bleeding.

Since ESHD is exquisitely sensitive to changes in loading conditions and contractility, the goals of induction of anesthesia are to maintain preload, afterload, heart rate, and contractility. The majority of ESHD patients have long-term IV access (e.g., PICC line) due to the need for chronic inotropic support. IV induction with etomidate (0.3 mg/kg), ketamine (1-2 mg/kg), or a combination of fentanyl (5-10 mcg/kg) and midazolam (0.05-0.1 mg/kg) is the usual approach to achieve the established hemodynamic goals. Preoperative inotropic therapy, usually milrinone, is continued during the induction

and pre-CPB period. Escalation of inotropic needs, such as adding epinephrine, is indicated in patients with evidence of poor systemic perfusion (e.g., low SvO_2, poor cerebral oximetry, or lactic acidosis). Maintenance of anesthesia is achieved with a balance technique of synthetic opioids, low-dose inhalation anesthetics, and non-depolarizing muscle relaxants.

In addition to standard ASA monitors, heart transplant patients need invasive hemodynamic monitoring (arterial and central line), cerebral oximetry, hourly diuresis monitoring, and TEE. Ultrasound-guided vascular access is needed in continuous-flow VAD patients due to a lack of pulsatility. In addition, ultrasound is invaluable to diagnose the patency of vessels.

CPB is accomplished by bicaval and aortic cannulation, mild hypothermia, and aortic cross-clamping for the left atrial and aortic anastomoses. The left heart is deaired under TEE guidance and the aortic cross-clamp is usually removed after completion of these anastomoses. After unclamping of the aorta and while rewarming, the IVC, pulmonary artery, and SVC are anastomosed. Exchange transfusion is used in infants with ABO incompatibility. Patients with CHD who have aortic arch hypoplasia or a prior Norwood procedure require deep hypothermia and aortic reconstruction with the donor arch under circulatory arrest or antegrade cerebral perfusion. Donor heart ischemic times are minimized with the goal of staying under 4 hours.

Once all anastomoses are completed and inotropes are started (milrinone and low-dose epinephrine), the patient is weaned off CPB. TEE is useful to assess ventricular function (especially RV function), visualize the venous anastomoses (exclude IVC/SVC stenosis), and rule out major valvar anomalies. iNO is used in patients with evidence of RV failure and at risk for pulmonary hypertension. Rarely, temporary VAD and/or ECMO are needed in case of primary graft dysfunction. The majority of the patients are kept intubated postoperatively until the transplanted heart function is stable and coagulation abnormalities are corrected. Dexmedetomidine is often used for postoperative sedation. Although previously a standard medication, the use of isoproterenol has been in decline because of supply shortages, but may constitute an adjuvant for chronotropy and even inotropy when pacing and standard inotropes are insufficient.

Table 44-2 describes some anesthetic and postoperative considerations on patients after heart transplantation.

Posttransplant Surveillance

Following heart transplantation, patients recover postoperatively as any other surgical patient. Patients are immunosuppressed, which increases the risk of infection and changes the use of other drugs which may interact with their immunosuppression drugs. Unless the donor and recipient are both cytomegalovirus (CMV) negative, CMV prophylaxis is required. This includes administration of CMV immunoglobulin (Cytogam®) early posttransplant and every 2 weeks posttransplant for the first 3 months. Patients also receive daily IV ganciclovir and are then transitioned to PO valganciclovir when appropriate, and continue for the first 3 months.

Patients must undergo surveillance for rejection. Routine surveillance biopsies are performed at 2, 4, 8 and 12 weeks after transplant. An additional biopsy is performed

Table 44-3. TCH cardiac transplant steroid protocol.

Intraoperatively	Methylprednisolone[a] 10 mg/kg/dose	Every 12 hours while in OR
POD # 1	Methylprednisolone[a] 5 mg/kg/day	Divided in 3 doses
POD # 2	Methylprednisolone[a] 2.5 mg/kg/day	Divided in 3 doses
POD # 3-6	Methylprednisolonea[a] or oral prednisone[b] 1 mg/kg/day	Divided in 2 doses
POD # 7-13	Methylprednisolone[a] or prednisone[b] 0.8 mg/kg/day	Divided in 2 doses
POD # 14	Prednisone 0.5 mg/kg/day	One dose
	NO REJECTION	**REJECTION (only one)**
1 month	Prednisone[b] 0.4 mg/kg daily	0.5 mg/kg daily
2 months	Prednisone[b] 0.3 mg/kg daily	0.4 mg/kg daily
3 months	Prednisone[b] 0.2 mg/kg/daily	0.3 mg/kg daily
4 months	Prednisone[b] 0.2 mg/kg/daily	0.2 mg/kg daily
6 months	Prednisone[b] 0.1 mg/kg daily	0.1 mg/kg daily
8 months	Prednisone[b] 0.05 mg/kg daily	
9 months	Prednisone[b] 0.05 mg/kg every other day	
10 months	STOP	

Dosing guidelines for steroids: Use 50 kg as max weight – initial postoperative dose should not exceed 250 mg. Chronic/recurrent rejection within the first year will require individualized wean.
[a] Intravenous administration. [b] Oral administration.
POD: postoperative day.

at 6 months posttransplant and then annually, beginning one year after transplant. Patients <7 kg are monitored noninvasively without biopsy.

Surveillance biopsies for younger patients are usually done under general anesthesia. Patients older than 8-12 years old are catheterized under sedation with spontaneous ventilation. This is commonly achieved with a combination of propofol, ketamine, and/or dexmedetomidine.

Acute cellular rejection is determined by the pathologist using light microscopy and is scored according to the revised International Society for Heart and Lung Transplantation (ISHLT) biopsy grading system as 0R (no rejection), 1R (mild rejection), 2R (moderate rejection), or 3R (severe rejection). Rejection scores 2R or 3R require treatment with enhanced immunosuppression. Antibody-mediated or humoral rejection (AMR) is determined by immunostaining for C4d deposition in a vascular pattern within the biopsy and by corroboration of donor specific antibodies (DSA) when C4D positive.

Patients are also seen between their biopsies for the first year posttransplant at varying intervals. Following the first year posttransplant, patients are routinely seen every four months, twice during the year for clinic visits, and once for cardiac catheterization and biopsy.

Table 44-4. TCH posttransplant medication protocol.

Tacrolimus Start 48 hours posttransplant. Dose start at: 0.08/mg/kg/day BID PO/NG. Therapeutic levels: • 0-12 months: 10-12 ng/mL • 1-2 years: 8-10 ng/mL • >3 years: 6-8 ng/mL
Cyclosporine (CYA) Start 48 hours posttransplant if not able to take Tacrolimus PO/NG or previously on CYA. Dose start 1 mg/kg/24hrs continuous IV (levels usually ~200 ng/mL). When used as chronic oral immunosuppressive, therapeutic levels: • 1st 3 months: 300-350 ng/mL • 3-12 months: 250-300 ng/mL • 1-2 years: 200-250 ng/mL • >3 years: 150-200 ng/mL
Mycophenolate Start immediately pretransplant and continue posttransplant. Dose start at: 20 mg/kg/dose IV/PO every 12 hours. Max dose: 1500 mg. If WBC 4,000-5,000 /mcL, reduce therapy by 50%.
Steroids Start intraoperatively and then continue posttransplant per protocol.
CMV therapies Only for donor- and recipient-positive and when there is donor and recipient mismatch. • **Cytogam®.** Give within 24-48 hours post-transplant. Dose: 150 mg/kg/dose every 2 weeks for the 1st three months. • **Ganciclovir.** Give 48-72 hours posttransplant (1 day after Cytogam). Dose: 5 mg/kg/dose IV Q12 hours. Need to adjust dose for abnormal kidney function.
Sirolimus Not immediately after transplant. Usually added when there is posttransplant coronary artery vasculopathy or for renal sparing. Usual level: 2-5 ng/mL If used in conjunction with CYA or tacrolimus: • CYA: run CYA level 80-120 ng/mL. • Tacrolimus: run Tacrolimus + Sirolimus (combo) at 10-12 ng/mL

BID: bis in die (twice a day), CMV: cytomegalovirus, CYA: cyclosporine, NG: nasogastric, PO: per os (by mouth).

Immunosuppression and Management of Rejection

Routine immunosuppression at TCH includes mycophenolate mofetil (Cellcept®) 20 mg/kg IV given pretransplant and every 12 hours thereafter, as well as methylprednisolone 10 mg/kg/dose given intraoperatively and every 12 hours. Postoperatively, steroids are weaned according to protocol (Table 44-3). When the patient can tolerate enteral administration, tacrolimus (Prograf®) is started. Dosing is highly variable dependent upon absorption and metabolism. The starting dose is 0.08 to 0.1 mg/kg/day divided every 12 hours and levels are required to establish a therapeutic dose. Tacrolimus dosing is highly affected by other medications, particularly antibiotics. Therapeutic target tacrolimus levels are based on time out from transplant (Table 44-4). Initially, we attempt to achieve serum levels of 10 to 12 ng/mL. Given its WBC-count suppression

properties, Cellcept® dosing is determined using WBC (target >4,000 cells/μL) rather than serum level.

Empirically, rejection treatment is started with IV methylprednisolone 10 mg/kg/dose for a total of 4 doses (every 8 hours). Additional treatment of rejection is determined by endomyocardial biopsy results. In grade 2R acute cellular rejection with normal cardiac function, no additional therapy is required. If a patient has grade 2R cellular rejection with hemodynamic compromise or grade 3R acute cellular rejection, a course of antithymocyte globulin is typically required for 3 to 7 days. If a biopsy suggests the presence of AMR, additional therapy is required and is directed at both the reduction of circulating anti-HLA antibody (plasmapheresis) and prevention of additional production of anti-HLA antibody (IV immunoglobulin G). To prevent further production, patients typically receive rituximab, which is a monoclonal antibody directed at CD20-positive B lymphocytes. Circulating B-cell elimination is accomplished with 1 to 4 doses provided on a weekly basis. A repeat biopsy following treatment of both acute cellular rejection or AMR is typically performed to determine therapeutic effect. In cases of unrelenting AMR, eculizumab (C5 complement protein blocker) or bortezomib (proteasome inhibitor to target plasma cells) may be used.

Outcomes and Complications

Transplant outcomes include waitlist mortality and posttransplant outcomes. In general, the higher the pretransplant complexity, the higher the risk of waitlist mortality. At TCH, there has been a substantial improvement in waitlist survival with the introduction of VAD support as a bridge to transplant. There are 2 groups of patients in whom waitlist mortality remains suboptimal; one subset is neonates/infants with complex single ventricle on which VAD support options are limited, and the other is small infants with cardiomyopathy on which VAD support has been offered less frequently over time.

In terms of posttransplant outcomes, there has been a substantial improvement in early mortality. Such improvement is likely multifactorial and includes better donor selection, organ preservation, and perioperative management. Late outcomes saw dramatic improvement following the introduction of cyclosporine in the 1980s, but nothing as significant since. Chronic rejection and/or transplant coronary vasculopathy are the primary reasons for late attrition. TCH-specific outcome data are publically available online (https://www.srtr.org/transplant-centers/texas-childrens-hospital-txtc/?organ=heart&recipientType=adult&donorType=).