The international society of heart and lung transplantation guidelines for the care of heart transplant recipients

Task Force 1: Peri-operative Care of the Heart Transplant Recipient (Aug. 4, 2010)

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Topic 1: Surgical Issues Impacting Care in the Immediate Post-operative Period

Introduction

This section deals with surgical issues that may potentially complicate the immediate post-transplant period. Many of these issues, particularly ones that arise in patient selection can have a very important impact on the immediate post-operative course of the patient and some can have far reaching consequences for long-term graft and patient survival. Donor-recipient matching refers to the avoidance of size discrepancies that can impair graft function. However, in the broader sense, donor factors, particularly ones that might have an adverse impact on graft function, need to be viewed in the context of the recipient’s condition. These factors include the urgency of transplantation, the presence of comorbid disease and the adequacy of physical reserves in the recipient, which are important considerations in the context of the recipient’s ability to tolerate a post-operative course that may be complicated by impaired graft function as the direct result of transplantation of a marginal donor heart. The projected ischemic time is another important variable in decision making regarding the use of a particular donor heart. The projected ischemic time is also emblematic of an important axiom in donor selection and matching to a specific recipient—and that is that factors that may adversely impact post-operative graft function should not be considered in isolation. For example, the use of a heart from a donor who died of toxicity (such as carbon monoxide) should be considered together with other important factors that have potentially compounding adverse effects, such as older donor age and longer rejected ischemic time. Although the techniques of donor heart procurement and implantation are standardized, there are factors such as the method of myocardial preservation and technique of donor heart implantation (biatrial versus bicaval technique) that may influence the post-heart transplant (HT) period. Post-operative complications such as sternal wound infection and pericardial effusion may cause the patient’s convalescence to be prolonged.

Donor Heart Selection

Brain death is a hostile environment for the donor heart that undoubtedly contributes to the occurrence of primary graft failure (PGF) after HT. Donor heart dysfunction results from the “catecholamine storm” (hypertension, tachycardia, and intense vasoconstriction) that produces an increase in myocardial oxygen demand and potentially myocardial ischemia. These phenomena may mediate myofibrillar degeneration, a process characterized by injury and death of myofibers in a hypercontracted state. After dissipation of this intense sympathetic activity, there is loss of sympathetic tone with a massive reduction in systemic vascular resistance, which may contribute to a second phase of potential myocardial injury, precipitated by abnormal myocardial loading conditions and impaired coronary perfusion. Myocardial injury interacts with other factors such as older donor age and longer ischemic time, increasing the probability of post-operative primary graft dysfunction.

Donor Age

Older donor age has been identified as a risk factor for death from any cause and from early graft failure, and it compounds the influence of other risk factors for death from early graft failure such as donor left ventricular (LV) dysfunction, longer ischemic time, and size mismatch (smaller donor to a larger recipient). The impact of older donor age is a reflection of the general decline in myocardial reserves occurring with advancing age as well as the use of older donor hearts for marginal recipients. Furthermore, older donor hearts may be less able to withstand primary graft dysfunction and early acute HT rejection.

Early in HT the upper donor age limit was 35 years, but over the ensuing 4 decades it has progressively risen with the routine use of donors older than 40 years and frequently ≥ 50
years. A safe “older donor age” has not been established. Studies usually employ artificial age cutoffs (such as 40 or 50 years) so that assignment of a 41-year-old donor to the “older group” may not provide accurate information regarding the effects of older donor age on post-HT outcomes. Furthermore, the impact of older donor age cannot be decoupled from recipient risk factors that can influence early post-HT survival. Some studies\(^3\) demonstrated inferior 1-month survival in recipients receiving hearts from donors older than 40 or 50 years of age than in those receiving hearts from donors younger than 40 years. However, other studies\(^5\) showed similar 30-day or discharge mortality in recipients of donor hearts older than 50 years versus those and in those receiving younger donor organs (5% versus 3.5%).

**Recommendations on Donor Heart Selection\(^2\)\(^,\)\(^3\):**

**Class IIa:**

1. Taking into consideration only the variable of “donor age,” the hearts of donors younger than 45 years will invariably have sufficient reserves to withstand the rigors of HT even in settings of prolonged ischemic time, recipient comorbidities, and multiple previous recipient operations with hemodynamically destabilizing bleeding. Hearts from donors between the ages of 45 to 55 years should probably be used when the projected ischemic time is ≤ 4 hours and the potential recipient does not have comorbidities or surgical issues where anything less than robust donor heart performance could prove fatal. The use of donor hearts > 55 years should only be used if the survival benefit of HT for a recipient unequivocally exceeds the decrement in early HT survival due to transplantation of a heart with limited myocardial reserves.

**Level of Evidence:** B.

**Transplantation of Hearts from Donors with Infection**

The reluctance to use hearts from donors contaminated with microorganisms, who have died of sepsis or central nervous system infection, is based on: (1) the potential transmission of microorganisms to the recipient resulting in either infection of anastomotic suture lines or systemic infection, (2) potential transmission of mediators of endotoxic shock from donor to recipient, and (3) contribution of donor sepsis to myocardial dysfunction.\(^6\)\(^,\)\(^8\) Serious complications due to the transmission of donor infection to a recipient have included arterial anastomotic rupture in a renal transplant patient (Staphylococcus aureus\(^9\) and Bacteroides species,\(^10\) Escherichia coli\(^10\)) and recipient entero-abdominal fungal infection after a pancreatic transplant (Candida albicans\(^11\)). Nevertheless, hearts from donors with severe sepsis and death due to severe infection (meningitis, pneumonia, or septic shock) without transmission to recipients\(^6\)\(^,\)\(^12\)\(^,\)\(^17\) as well as the use of hearts with bacterial and fungal contamination,\(^14\)\(^-\)\(^16\) have been used. Overall the risk of donor to recipient transmission appears to be very low.

**Recommendation on the Transplantation of Hearts from Donors with Infection\(^6\):**

**Class IIa**

1. Hearts from donors with severe infection can be used provided that: 1) the donor infection is community acquired and donor death occurs rapidly (within 96 hours); 2) repeat blood cultures before organ procurement are negative; 3) pathogen-specific antimicrobial therapy is administered to the donor; 4) donor myocardial function is normal; and 5) there is no evidence of endocarditis by direct inspection of the donor heart. If such hearts are used for transplantation, the recipient should undergo surveillance blood cultures on the first post-operative day and pathogen-specific antibiotic therapy should be administered for an appropriate duration of time.

**Level of Evidence:** C.

**Transplantation of Hearts from Donors with Potential Drug Toxicities**

**Cocaine.** Toxic effects on the heart include vasoconstriction, coronary endothelial dysfunction, and myocardial toxicity. These effects occur through a powerful \(\alpha\)-1 adrenergic effect, indirectly through release of norepinephrine by the sympathetic nervous system, an induced deficiency of endothelium-derived relaxation factor with the potential for intravascular thrombosis, and depression of myocardial contractility.\(^17\)\(^-\)\(^21\) The most frequently observed cardiac abnormalities after repeated cocaine abuse are ventricular hypertrophy and a cardiomyopathy. Since intravenous (IV) cocaine as compared to non-IV cocaine abuse is considered more toxic to the heart, the use of hearts from IV cocaine abusers is discouraged. Use of hearts from donors with a history of non-IV cocaine abuse appears to be safe in terms of early post-operative course. Data from the United Network for Organ Sharing (UNOS) suggest that 1-year HT mortality is similar for recipients of hearts from non-users versus past users (> 6 months) or current users of cocaine.\(^22\)\(^-\)\(^29\)

**Alcohol abuse.** Direct toxic effects of ethanol on the heart include alterations in energy stores reducing the effectiveness of calcium uptake by the sarcoplasmic reticulum,\(^23\)\(^,\)\(^24\) and sodium-potassium adenosine triphosphatase (ATPase) activity, and interference with calcium-troponin binding, all of which
attenuate myosin-actin interaction. Transplantation of a heart from a donor with a history of alcohol abuse may unmask biochemical abnormalities that may manifest as early graft failure. Survival (including early patient survival and graft function) has been shown to be inferior in recipients of hearts from donors with a history of alcohol abuse. However, one report suggests that alcohol use in donors may be protective after HT with improved outcomes for hearts from alcoholic versus non-alcoholic donors.

Carbon monoxide poisoning. As a result of the much greater affinity of carbon monoxide versus oxygen for hemoglobin, a leftward shift of the oxygen-hemoglobin dissociation curve occurs with reduced oxygen delivery to the tissues and impairment of mitochondrial cellular respiration due to competition of carbon monoxide with oxygen for cytochrome a. The myocardium is particularly susceptible to oxygen deprivation and the resulting myocardial injury may manifest as PGF in the immediate post-operative period. Reports on the outcomes of hearts from donors with carbon monoxide intoxication have yielded conflicting results.

Other poisonings. There are reports of transplantation of hearts from donors with a variety of other types of poisonings including cyanide, methanol, and ecstasy with satisfactory HT function. The hearts from donors with these types of poisonings may be considered for HT provided there is good cardiac function.

Recommendation on the Transplantation of Hearts from Donors with Potential Drug Toxicities:

Class IIa:

1. Hearts from donors with a history of past or current non-IV cocaine abuse can be used for transplantation provided cardiac function is normal and left ventricular hypertrophy (LVH) is absent.
   
   Level of Evidence: C.

2. In light of current information, the use of hearts from donors with a history of “alcohol abuse” remains uncertain, but is should probably be considered unwise.
   
   Level of Evidence: C.

3. The use of hearts from donors who have died of carbon monoxide intoxication can be recommended with caution, although safety has not been completely established. It is recommended that these hearts be used provided there is a normal donor electrocardiogram (ECG) and echocardiogram, minimal elevation of cardiac markers, minimal inotropic requirements, a relatively short ischemic time, a favorable donor to recipient weight ratio, and a recipient with normal pulmonary vascular resistance.
   
   Level of Evidence: C.

Use of Donors with Pre-existing Cardiac Abnormalities

Coronary artery disease. The concern regarding transplantation of donor hearts with recognized or unrecognized coronary artery disease (CAD) revolves around the risk of acute graft failure and the subsequent development of coronary allograft vasculopathy (CAV). There is a paucity of information in the literature to provide guidance as to how much CAD in a donor heart can be accepted without increasing the risk of early graft failure. One report suggests that if donor hearts with more than single-vessel CAD are used, the risk of early graft failure is substantial (6.3% in donors without CAD, 7.5% in donors with single-vessel CAD, 42.3% in donor hearts with double- and triple-vessel CAD).

Donor left ventricular hypertrophy. The reluctance to use donor hearts with LVH is based on the increased risk of early graft failure and the long-term effects of diastolic heart failure and suboptimal long-term survival. The probability that LVH will produce early graft failure is influenced by other confounding factors such as history of hypertension, ischemia time, severity of LVH, donor size, and whether or not LVH is evident on ECG. One small study raised concerns that any degree of donor heart LVH may result in early graft failure. A more recent study, however, found that mild and even moderate LVH did not increase 30-day mortality. Early mortality was increased only if donor wall thickness was > 14 mm.

Donor valvular heart disease. The finding of a bicuspid aortic valve does not contraindicate the use of a donor heart. In the case valvular disease associated with hemodynamic abnormalities, the donor heart may still be used for HT. Bench repair or replacement of a donor aortic valve and repair of an incompetent mitral valve has been performed with favorable outcomes.

Recommendations on the Use of Donors with Pre-existing Cardiac Abnormalities:

Class I:

1. As far as function is concerned, a donor heart should not be used in the presence of intractable ventricular arrhythmias, the need for excessive inotropic support (dopamine at a dose of 20 µg/kg/min or similar doses of other adrenergic agents despite aggressive optimization of preload and after load), discreet wall motion
abnormalities on echocardiography, or left ventricular ejection fraction (LVEF) < 40% despite optimization of hemodynamics with inotropic support.

**Level of Evidence: B.**

2. A donor heart with a normally functioning bicuspid aortic valve can be used for HT. Anatomically and hemodynamically abnormal aortic and mitral valves may undergo bench repair or replacement with subsequent transplantation of the heart.

**Level of Evidence: C.**

**Class IIa:**

1. The use of donor hearts with obstructive disease in any major coronary artery should be avoided unless the heart is being considered for the alternate list recipients with concomitant coronary bypass surgery.

**Level of Evidence: C.**

2. It would seem appropriate to use hearts from donors with LVH provided that it is not associated with ECG findings of LVH and LV wall thickness is < 14 mm.

**Level of Evidence: C.**

**Donor Cardiac Function**

Donor risk factors known to be associated with early graft failure include higher doses of inotropic support, depressed systolic function (particularly discreet wall motion abnormalities), older donor age, and donor-recipient size mismatch (small female donors to large male recipients). In one study, the requirement for dopamine or dobutamine doses > 20 µg/kg/min with or without additional inotropic agents was an independent risk factor for PGF and early mortality. However, because high dose inotropic support is often required to overcome the hemodynamic consequences of a low systemic vascular resistance, optimization of preload and afterload should be achieved before declaring that high dose inotropic agents is a contraindication to the use of a donor heart. Elevated cardiac markers such as CPK-MB isoenzyme and troponin should not preclude the use of a donor heart. If substantial myocardial injury is associated with the release of cardiac markers, this will usually be manifested by the echocardiographic finding of either global or discreet wall motion abnormalities.

**Recommendations on Donor Cardiac Function:**

**Class I:**

1. As far as the function is concerned, a donor heart should not be used in the presence of intractable ventricular arrhythmias, the need for excessive inotropic support (dopamine at a dose of 20 µg/kg/min or similar doses of other adrenergic agents despite aggressive optimization of preload and after load), discreet wall motion abnormalities on echocardiography or LVEF < 40% despite optimization of hemodynamics with inotropic support.

**Level of Evidence: B.**

**Donor-Recipient Size Matching**

Oversizing of a donor heart can occur (1) in pediatric HT when the size of the donor heart for a smaller recipient is misjudged; (2) when the native heart disease does not result in cardiomegaly and a larger donor heart is implanted; or (3) after multiple previous operations resulting in rigidity of the mediastinum despite maneuvers such as opening the left side of the pericardium to allow the donor heart to protrude into the left pleural space. These situations may be associated with inability to close the chest without hemodynamically important cardiac compression. Severe undersizing is also an important issue, since a small donor heart may be unable to support the circulation of a much larger recipient. Making the determination of the adequacy of the size of a donor for a specific recipient and judgment is required. Determination of donor/recipient size match is complicated by the poor relationship between echocardiographic adult heart size and body weight. As a general rule, the donor weight should be within 30% of the recipient weight for adults. However, in non-urgent recipients survival was not adversely affected by undersizing of donor hearts up to a donor to recipient body weight ratio of 0.8. In contrast, survival was inferior in UNOS status 1 recipients, if they received an undersized heart presumably due to a smaller cardiac reserve. According to a multivariable analysis, implantation of a smaller female donor heart into a larger male recipient was an independent risk factor for early graft failure. Furthermore, the risks of undersizing a donor heart are compounded by the presence of other donor risk factors contributing to early graft failure, such as older donor age, abnormal systolic function of the donor heart and prolonged ischemic time.

**Recommendations on Donor-Recipient Size Matching:**

**Class I:**

1. As a general rule the use of hearts from donors whose body weight is no greater than 30% below that of the recipient is uniformly safe. Furthermore, a male donor of average weight (70 kg) can be safely used for any size recipient irrespective of weight. Use of a female donor whose weight is more than 20% lower than that of a male recipient should be viewed with caution.

**Level of Evidence: C.**
Projected Ischemic Time

Prolongation of the ischemic time in HT adversely impacts the performance of the donor heart in the immediate post-operative period. Furthermore, the ischemic time interacts with a number of other variables including older donor age, increased inotropic requirements of the donor, and abnormal donor cardiac function to further increase the probability of primary graft dysfunction. The upper limit for ischemic time is unknown and it depends on the relative weight of other risk factors. For example, a heart of a young donor with robust performance without inotropic requirements is likely to tolerate an ischemic time longer than 6 hours with good post-operative graft function, whereas a donor heart with impaired function on substantial inotropic support from an older donor is unlikely to tolerate longer ischemic times.

Recommendations on Ischemic Times

Class I:

1. As a general rule the ischemic time should be less than 4 hours. However, there are situations in which ischemic times longer than 4 hours are anticipated. Donor hearts with ischemic times longer than 4 hours should only be accepted when other factors interacting with ischemic time are ideal, including donor young age, normal cardiac function and absence of inotropic support.

Level of Evidence: C.

Donor Heart Procurement

The procedure of donor heart procurement is as critical for the success of HT as implantation, because errors in assessment, selection, and surgical technique may have profound repercussions in the immediate post-transplant period. The procuring surgeon must verify that the function of the heart is visually satisfactory, that areas of akinesis are absent on the echocardiogram, and that the size match for the intended recipient is appropriate. The heart should be carefully inspected for palpable CAD and evidence of myocardial contusion so that if these problems are found a decision can be made about the suitability of the donor heart for the intended recipient. Post-operative right ventricular (RV) failure can result in RV distention during the procurement procedure and significantly complicate recipient management. This can occur because of overly vigorous fluid infusion in response to blood and fluid loss during abdominal organ procurement. After excision, it is important that the heart be thoroughly inspected, although most abnormalities (such as a patent foramen ovale, bicuspid aortic valve) do not significantly alter the immediate post-operative period. Atresia of the coronary sinus ostium with retrograde drainage through a persistent left superior vena cava may go unnoticed until inspection or implantation of the donor heart. Unfortunately, ligation of the left superior vena cava in the presence of this anomaly is highly likely to result in irreversible PGF. The procuring surgeon can simply look into the right atrium to verify the presence of a coronary sinus ostium.

The adequacy of myocardial preservation, the biochemical derangements that can be induced during the ischemic period, and unpredictable myocardial reperfusion injury may have profound effects on the immediate post-operative course. It is the complex bioenergetic processes and their derangement which will frequently underpin PGF. The primary methods of maintaining cellular and functional integrity of the myocardium during the ischemic period are through hypothermia and mechanical arrest of the heart. Adenosine triphosphate (ATP) is consumed at a low level to allow breaking of actin-myosin cross bridges even during mechanical cardiac arrest. Although during the ischemic period the myocardium can use stored glycogen to produce ATP by anaerobic glycolysis, irreversible myofiber contracture will occur if the ATP level falls below a critical threshold. Preservation must also maintain ion homeostasis. Although sodium-potassium ATPase activity is markedly reduced by hypothermia, there is still passive ion movement down a concentration gradient. Consequently, intracellular hydrogen ions are exchanged for extracellular sodium ions, which in turn are exchanged for calcium ions. Accumulation of calcium ions in the sarcolemma is potentially very damaging to myofibers upon reperfusion. Reperfusion injury has several components:

1. Free radical injury—these oxygen-derived free radicals cause direct myocardial injury. They are generated under normal aerobic conditions but are rapidly neutralized by intracellular enzymatic scavengers. However, under conditions of ischemia and reperfusion, they may accumulate in quantities that overwhelm the natural scavengers, setting the stage for free radical injury.
2. Complement activation—activation of the complement cascade results in the production of potent anaphylatoxins that mediate increased vascular permeability, leukocyte chemotaxis, adhesion and activation, and vascular smooth muscle contraction.
3. Neutrophil activation—neutrophil activation during reperfusion involves accumulation of these cells on endothelial surfaces and promoting the release of inflammatory molecules.
4. Endothelial injury—“endothelial cell activation” is a term used to describe the response of endothelial cells to
ischemia. It involves promotion of leukocyte adhesion, smooth muscle proliferation and vasoconstriction.

(5) Cytokine release—a number of molecules are released that amplify inflammatory responses.

(6) Calcium overload—as indicated earlier, calcium ions can accumulate in the sarcoplasmic reticulum damaging myocytes on reperfusion.

The role of myocardial preservation solutions in HT is to preserve the microvascular, cellular, and functional integrity of the heart. The ingredients of the flush solution include (1) hypothermia, (2) potassium to arrest the heart, (3) prevention of cellular swelling with impermeants such as lactobionate and raffinose, (4) magnesium to prevent calcium accumulation in the sarcoplasmic reticulum, and (5) free radical scavengers to prevent free radical injury. Experimental and clinical use of the UW solution, which is an intracellular (high potassium) solution that includes the above ingredients, have provided sufficient evidence to support the expectation of excellent myocardial preservation for at least 6 hours of ischemic time.

Donor Heart Implantation

Implantation of the donor heart is a technically straightforward procedure. The standard biatrial technique is increasingly being replaced by the bicaval technique. The latter may be associated with a lower incidence of sinoatrial node dysfunction in the early post-operative period and reduced requirement for permanent pacing at 30 and 90 days after HT.

One technical point that requires emphasis is the importance of accurately cutting the correct length of the pulmonary artery because excessive length can result in pulmonary artery kinking and obstruction and, if unrecognized, this can result in severe RV failure. The conditions of reperfusion of the donor heart are important with regard to the pressure. Ideally, the heart should be reperfused at a perfusion pressure of 50 to 70 mm Hg. Very occasionally, the perfusion pressure can be excessively low (< 50 mm Hg) despite the infusion of vasoactive agents. Under those circumstances, the heart may not develop prompt return of coordinated contraction. If this occurs, controlled aortic root reperfusion may be used. This involves reapplying the aortic crossclamp and infusing pump blood into the aortic root through the needle vent to produce a pressure of 70 to 80 mm Hg until satisfactory cardiac function develops, at which time the crossclamp can be removed.

Post-operative Surgical Problems

Surgical wound infection. Infection is an important cause of mortality and morbidity after HT. Bacterial infection predominates in the early post-transplant period with a peak incidence in the first post-operative week. Although the incidence of sternal wound infection and mediastinitis after HT is low, it can be the cause of serious morbidity and mortality. The cornerstone of prevention of bacterial infection and contamination of the surgical wound is application of strict surgical aseptic techniques. All indwelling lines and devices should receive similar aseptic care. Protective isolation has not been proven beneficial in reducing the incidence of infection in HT recipients. Peri-operative prophylactic antibiotics should be administered. An example of a commonly used protocol is a pre-operative IV dose of vancomycin 15 mg/kg and ceftazidime 15 mg/kg both administered 1 hour before HT to ensure effective circulating levels before the skin incision. Vancomycin is re-administered at the conclusion of cardiopulmonary bypass (CPB) at a dose of 10 mg/kg. Post-operatively, vancomycin (10 mg/kg IV every 8 hours with adjustment for renal function) and ceftazidime 1 gm IV every 8 hours are administered for 4 days. At the conclusion of the operation, the surgical wound may be irrigated with dilute vancomycin solution to decrease colony counts of gram-positive skin organisms. The surgical dressing is left in place for 48 hours, and after its removal, the wound is painted with an iodine containing solution once or twice daily for several days until the wound is sealed.

Re-entry for bleeding may be required after HT. In most patients undergoing HT, the operation is performed in the setting of one or more risk factors for bleeding including coagulopathy associated with multiple previous operations, use of mechanical circulatory support (MCS), poor tissues due to the ravages of heart failure, and abnormal coagulation due to hepatic congestion. Re-entry should be undertaken for persistent chest tube output (as a general rule 400 mL/hr for 1 hour, > 300 mL/hr for 3 hours, and 200 mL/hr for 4 hours), any circulatory instability associated with bleeding, or radiographic or echocardiographic evidence of retained thrombus.

Frequently, patients undergoing HT have a large pericardial space in which a much smaller donor heart is implanted, setting the stage for the accumulation of frequently large pericardial effusions. This has been described in up to 30% of patients. If a pericardial effusion is anticipated given a large pericardial space and a much smaller heart, a soft drain such as a Blake drain can be left in the posterior pericardial space connected to a drainage bulb and can be left for 5 to 6 days (the standard chest tubes are removed at the usual time) to prevent, as much as possible, collection of fluid in the pericardium. The Blake drain is removed when the drainage is < 40 mL/24 hours. If a large pericardial effusion occurs, even
in the absence of echocardiographic evidence of tamponade, drainage by a subxiphoid approach is recommended.

**Topic 2: Early Post-operative Care of the Heart Transplant Recipient**

**Introduction**

Early post-operative management of the newly transplanted heart allograft is focused on maintenance of hemodynamic stability as the allograft restores normal cardiac function to the chronic heart failure patient. While the graft begins to support the recipient as soon as separation from CPB is complete, there is invariably a period of time during which the allograft and its recipient require active hemodynamic management and support. The nature and duration of this support is determined by several factors including the quality and preservation of the donor heart and pre-operative condition of the recipient. Recipient factors such as vasomotor tone, severity and reversibility of pulmonary vascular hypertension, pulmonary function, degree of pre-operative fluid overload, renal function, destabilizing post-operative bleeding, and immunologic compatibility may have a profound effect upon early post-operative management. Additional factors such as HT surgical technique (biatrial vs. bicaval vs. orthotopic vs. heterotopic) and donor/recipient size matching affect post-operative management strategies.

**Peri-operative and Post-operative Monitoring**

**Hemodynamic Monitoring**

Adequate hemodynamic monitoring of the HT recipient at a minimum includes direct measurement of the arterial pressure, central venous pressure (CVP) or right atrial pressure (RAP), and cardiac output (CO). Typically, adult patients are monitored with an indwelling arterial catheter (femoral, radial, or both), and a thermodilution or oximetric pulmonary artery catheter. Less commonly used are surgically placed, percutaneous right and left atrial catheters, or noninvasive means of assessing CO. One such method utilizes lithium chloride as indicator for peripheral thermodilution technique.65 Regardless of the type of catheter used for continuous hemodynamic monitoring after HT, it is wise to remove the catheter as soon as possible to minimize the risk of catheter-related infections, including sepsis, allograft valvular endocarditis, or bacterial seeding of the atrial suture lines, complications which are often fatal.66, 67

Arterial monitoring is similar in pediatric patients, but CVP monitoring is generally with a line ending in the superior vena cava or an atrial catheter. Pulmonary artery catheters are used infrequently in the pediatric population.

**Echocardiographic Monitoring**

Intra-operative echocardiography has become a standard procedure during most cardiac surgery, including HT.68 Transesophageal echocardiography (TEE) can provide imaging assistance to identify intracardiac thrombi. In addition, TEE provides real-time assessment of the cardiac allograft during de-airing, separation from CPB, and after implantation of the donor heart as the chest is closed. Ventricular function, valve function, and surgical anastomoses can be assessed. In the post-operative period, both transthoracic echocardiogram (TTE) and TEE may be used to assess heart allograft function, particularly in the setting of acute hemodynamic instability arising from allograft dysfunction due to rejection, RV failure, or tamponade.69-71

When adequate transthoracic imaging is limited by poor acoustic windows, TEE often overcomes this obstacle. TTE is generally adequate in the pediatric population in the post-operative period. It is reasonable to perform a TTE in the first week after HT. The timing and frequency of additional echocardiograms depends upon heart allograft function and the presence of a pericardial effusion.

**Electrocardiographic Monitoring**

Continuous ECG monitoring is universal. Twelve-lead recordings are obtained immediately post-operatively and as needed to assess the cardiac rhythm, conduction system, and ischemic changes. Several ECG abnormalities are frequently present following HT. The most frequent abnormalities include sinus node dysfunction and complete or incomplete right bundle branch block. Progressive worsening of the conduction system in the early period after HT is a poor prognostic sign.72, 73

**Continuous Oxygen Saturation Monitoring**

Continuous pulse oximetry is indicated in the immediate post-operative period to insure adequate oxygenation at all times, particularly because the critically ill early post-operative patient is at risk for sudden changes in pulmonary status.

**Renal Function**

An indwelling urinary catheter is used to monitor renal function and urine output.

Adequacy of urine output depends upon several factors including fluid status, heart allograft function, intrinsic renal function, recent hemodynamic status, and the presence of nephrotoxic and vasoconstrictive medications such as calcineurin inhibitors (CNI) and vasopressors. Urine output typically is \( \geq 30 \text{ mL/hour} \).
In the pediatric population, adequate urine output is age and size dependent. Oliguria or anuria are particularly concerning as they are suggestive of significant acute renal failure.

Often, higher doses of IV loop diuretics are required after HT due to pre-existing diuretic resistance. Oliguria refractory to diuretics is problematic in the immediate post-operative setting because fluid overload and RV dysfunction can develop over a few hours unless ultrafiltration and renal replacement therapies such as continuous veno-venous hemofiltration or dialysis are employed.

**Recommendations on the Post-operative Monitoring of Heart Transplant Recipients**

*Class I:*

1. Peri-operative monitoring of heart transplant recipients should include (1) continuous ECG monitoring; (2) post-operative 12-lead ECG; (3) invasive arterial pressure monitoring; (4) direct measurement of RAP or CVP; (5) measurement of left atrial or pulmonary artery wedge pressure (PAWP); (6) intermittent measurement of CO; (7) continuous measurement of arterial oxygen saturation; (8) intra-operative TEE; (9) continuous assessment of urinary output.

   **Level of Evidence: C.**

**Hemodynamic Management**

*Background*

The newly transplanted heart allograft typically displays excellent LV systolic function. Systolic LV dysfunction is particularly worrisome as it may suggest poor donor heart quality, inadequate preservation, or early rejection (hyperacute, antibody mediated rejection). The frequency and severity of RV dysfunction after HT is variable and may be anticipated in patients with risk factors such as elevated pulmonary vascular resistance (PVR), excessive bleeding, pulmonary edema, poor donor heart preservation before implant, poor RV protection during allograft implantation, ischemia from air embolization into the right coronary artery, or significant donor/recipient size mismatch.

Even heart allografts that display excellent early function typically experience a functional decline over the first 12 post-operative hours. This decrease in function is believed to be due to the effects of ischemia and reperfusion and myocardial edema, which result in both systolic and diastolic dysfunction. Donor heart LVH (wall thickness ≥ 1.4 cm) and or prolonged ischemia times (≥ 240 min) may also lead to impaired diastolic function in the early post-operative period. With intra-operative TEE, it is not uncommon to observe an increase in LV wall thickness and mass. Furthermore, in the early post-operative period after HT, examination of the mitral inflow pattern by Doppler echocardiography often reveals a restrictive cardiac filling pattern.

Diastolic stiffness leads to an increase in intracardiac filling pressures and reduced stroke volume, whereas systolic dysfunction leads to a transient decline in CO. These early restrictive hemodynamic findings are often transient but may persist for 6 to 8 weeks after HT. In the setting of an excellent hemodynamic status, these changes are of little or no consequence. However, if the initial CO is marginal, or if the heart allograft function is obviously impaired, despite inotropic support, this further, predictable decline in function may necessitate additional hemodynamic support, including additional vasoactive drugs, an intraaortic balloon pump (IABP) or a left and/or right ventricular assist device (VAD). When deciding the minimum heart allograft function acceptable before leaving the operating room, considerations should include, in addition to the cardiac index (CI), the dose and number of inotropic agents employed to enable separation from CPB, the independent function of the RV and LV, and the recipient risks for right heart failure.

Heart rate is variable and ranges from bradycardia to tachycardia. Factors such as parasympathetic denervation, surgical trauma, catecholamine administration, and even genomic variations in the β-adrenergic receptor may affect the sinus node rate. Although sinus rhythm is typically observed, sinus node dysfunction may arise from injury related to donor cardiectomy or preservation. In this instance, the cardiac rhythm is usually either junctional or accelerated junctional. The incidence of sinus node dysfunction is reduced with the bicaval or total orthotopic HT technique, as compared to the classic biatrial technique developed by Lower and Shumway.

Sinus node dysfunction is usually transient but may persist for several weeks after HT. Sinus node dysfunction requiring a pacemaker occurs in about 5% of patients undergoing biatrial anastomoses. Pre-operative use of amiodarone in heart transplant recipients may increase the risk of sinus node dysfunction and bradyarrhythmias in the early post-operative period. This may require the use of isoproterenol, theophylline, or more prolonged temporary atrial pacing. The need for permanent pacing may increase with donor age. Heart rate is generally maintained in the 90 to 110 bpm range after HT using atrial or atrioventricular (AV) pacing or chronotrophic drugs. This rate contributes to maintaining an adequate CO and permits adequate cardiac filling in the setting of decreased stroke volume and diastolic dysfunction immediately after heart transplantation. In the setting of
significant donor under sizing with respect to the recipient (donor weight > 30% below recipient weight), a higher heart rate may be necessary to account for even lower stroke volume indices.52, 81, 95

In the pediatric population the heart rate adequate to maintain an acceptable CO also varies according to both donor and recipient age.

Reduced myocardial contractility is frequently seen after HT as a result of donor organ trauma, preservation and ischemia, catecholamine depletion, and donor brain death. In addition, myofibrillar degeneration can result from the sympathetic storm accompanying brain herniation. Infusion of one or more inotropes in the early post-operative period usually provides the hemodynamic support needed in the first few post-operative days as the heart allograft recovers. These agents are usually weaned over the first post-operative week.

Primary Graft Failure and Right Ventricular Dysfunction

Primary graft failure after HT is the presence of severe mechanical dysfunction without obvious anatomic (surgical) or immunologic causes such as hyperacute rejection. Primary graft failure has been variably defined in the literature as heart allograft dysfunction requiring 2 or more inotropes, or the need for mechanical circulatory support, either with an IABP or a VAD within 24 hours of HT. The true prevalence, therefore, depends upon the criteria used for diagnosis, but estimates range from approximately 1.4% to 30.7%.82, 83, 96-100 It is important to recognize that PGF can result in RV, LV, or biventricular failure.

Isolated RV failure is more common than biventricular failure. Cardinal features include an elevated RAP > 20 mm Hg, left atrial pressure < 10 mm Hg, with decreasing CO and high pulmonary artery (PA) pressures, and a falling mean arterial pressure, or normal PA pressures with falling CO.101, 102

Heart allograft failure accounts for 40% of the mortality within the first 30 days after HT and 18% of the mortality for the second through the twelfth months.98 Thirty-day survival with PGF has increased over time from 43% during the period from 1992 to 1997 to 57% during the period from 1998 to 2004.98 In addition to the increased risk of mortality during the first month, PGF also confers a worse conditional 1-year survival.81

The pathophysiology that underlies PGF is generally multifactorial. It includes recipient characteristics such as pulmonary arterial hypertension and increased PVR, and prior MCS, donor characteristics and factors such as prolonged donor ischemia time, poor organ preservation, and development of reactive oxygen species.82, 84, 97-99, 103

Possible explanations for the association between pre-operative MCS and PGF are that pretransplant VADs may be a surrogate of prolonged ischemia due to longer explantation of the native heart or that the longer CPB times associated with presence of a VAD may trigger a greater inflammatory response which may increase the risk of PGF.103

Early heart allograft dysfunction has also been associated with the use of organs from female donors into male recipients; however, in recent times the results of some studies have shown that increased body surface area in the recipient or smaller donor for a larger recipient have not been associated with worse outcomes.85, 98 There have been concerns that the use of “marginal” or “extended” donors may lead to an increased incidence of PGF. There are a number of criteria to define the “extended” heart donor. These can be grouped into non-cardiac and cardiac factors. Non-cardiac factors include advanced donor age, donor size, and ischemic time. In addition, other comorbidities of the donor, such as positive viral serologies, diabetes mellitus, or substance abuse would be considered as non-cardiac risks for suboptimal donor organ quality. The cardiac criteria for “extended” donors include LVH, congenital heart abnormalities, high donor catecholamine requirements, RV and/or LV systolic dysfunction and CAD.104 Lima et al. conducted a retrospective study of 260 HT patients with both standard and “extended” list donors.103 The “extended” list donors most commonly were older and had diabetes. They reported no difference in the incidence of PGF, with 23% in the standard group and 26% in the “extended” list. The two factors the authors identified as risk factors poorer outcomes were length of ischemia time and pre-operative MCS.

Assessment of graft function can be made by hemodynamic measurement, TEE, and gross visual inspection of the heart. The hemodynamic parameters that are suspicious for graft dysfunction are a CI < 2.0 L/min/m², a RAP > 15 mm Hg and a PCWP >15 mm Hg when on maximal inotropic support. The RV stroke work (RVSW) or RVSW index (RVSWI) [RVSWI = (mean pulmonary artery pressure [MPAP]-CVP)*(SVI)*0.0136] (g*m/m²) where 0.0136 converts mm Hg Hg-liters/beat beat-m to g*m/m², which have been used to assess RV function and likelihood of failure in a non-transplant VAD population105, 106 may be helpful in determining the appropriate time for institution of MCS (Table 1).
### Table 1  Functional Variables of the Right Ventricle

<table>
<thead>
<tr>
<th>Functional Parameters</th>
<th>Normal Value</th>
<th>Load Dependency</th>
<th>Mild RV dysfunction</th>
<th>Moderate RV dysfunction</th>
<th>Severe RV dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic Performance Variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVFAC (%)</td>
<td>32-60</td>
<td>+++</td>
<td>25-31</td>
<td>18-24</td>
<td>&lt; 17</td>
</tr>
<tr>
<td>RVEF (%)</td>
<td>45-68</td>
<td>+++</td>
<td>35-44</td>
<td>26-34</td>
<td>&lt; 25</td>
</tr>
<tr>
<td>TAPSE</td>
<td>&gt;15 mm</td>
<td>++</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tricuspid annular plane maximal systolic velocity (using spectral pulse wave tissue Doppler)</td>
<td>&gt; 12cm/s</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVA (using tissue pulsed wave Doppler)</td>
<td>1.4 ± 0.5 m/s²</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diastolic Performance Variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVC dimension (cm), collapse index</td>
<td>&lt; 1.7 cm, CI &gt; 50%</td>
<td>+++</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tricuspid early (E) to late (A) filling velocity ratio</td>
<td>1.5 ± 0.3</td>
<td>+++</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic vein profile (S:systolic; D: diastolic)</td>
<td>S/D velocity ratio &gt; 1, no S reversal, atrial reversal &lt; 50% S</td>
<td>+++</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVRT</td>
<td>&lt; 60 ms</td>
<td>+++</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid myocardial filling velocity (E) (cm/s)</td>
<td>15.6 ± 3.9</td>
<td>+++</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late diastolic myocardial filling velocity, A, (cm/s)</td>
<td>15.4 ± 4.5</td>
<td>+++</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined systolic and diastolic parameter RVMPI</td>
<td>0.28 ± 0.04</td>
<td>++</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IVA, isovolumic acceleration using Doppler tissue imaging; IVC, inferior vena cava; RV, right ventricle; RVEF, right ventricular ejection fraction; RVFAC, right ventricular fractional area change; RVMPI, right ventricular myocardial performance index; TAPSE, tricuspid annular plane systolic excursion; IVRT, isovolumic relaxation time.

Adapted from Haddad F. et al.107

Post-operatively, hemodynamically-significant RV dysfunction is one of the most serious complications that can occur after HT and it is associated with increased early and late mortality. Patients should be carefully screened and then monitored for the development of pulmonary vascular hypertension while waiting for a suitable donor organ to insure that the transpulmonary gradient (TPG) and PVR remain within an acceptable range.107-109 These criteria are detailed in the 2006 International Society for Heart and Lung Transplantation (ISHLT) Listing Criteria Guidelines.86 Knowledge of the pre-operative pulmonary hemodynamics may aid the planning of peri-operative strategies to avoid or better manage RV dysfunction. Pulmonary artery pressures may decline rapidly after HT and usually reach a new baseline by 1 year.87 Even when initially poor, RV function typically improves over time with proper support. It is during this early post-operative period when PA pressures are highest and RV function is poorest that overt RV dysfunction may develop and lead to cardiogenic shock. Timely and aggressive hemodynamic support during this time is essential. When pharmacologic therapy fails, prompt insertion of a right VAD is indicated and can provide support while RV dysfunction resolves.88

Several features may be present in patients with post-operative RV dysfunction after HT. First, there is an increased PVR that may be due to reversible pulmonary vasoconstriction as well as chronic changes due to remodeling of the pulmonary vasculature.110 Second, there is RV dysfunction due to either graft-related issues, such as ischemia, or PGF.88 Usually LV systolic and diastolic functions are adequate and thus LV end-diastolic pressure is low. In this instance RV dysfunction leads to a reduction in the LV stroke volume due
to inadequate LV filling. If significant LV dysfunction is present, there is the added feature of LV failure complicating RV failure. In addition to pharmacologic therapy, insertion of an IABP may effectively reduce LV afterload and improve RV perfusion.

Therapy, in general, is aimed at reducing RV afterload while maintaining an adequate but not excessive RV preload (CVP < 15 mm Hg). Inotropic support of the RV should also be provided; usually an IV drug with β-agonist properties is selected first. Mean arterial blood pressure must be maintained not only to insure end-organ perfusion but also to maintain RV perfusion, which occurs in systole as well as diastole. Mild RV dysfunction may be treated with inotropic agents and vasodilators such as nitroglycerine or nitroprusside. Systemic vasodilation leading to arterial hypotension or necessitating the addition of peripheral vasoconstrictors is a frequent limiting factor in the use of these agents. The ideal agent should selectively decrease PVR. At least equivalent, if not superior RV afterload reduction, with less systemic hypotension is achieved by the administration of prostaglandins. The only truly selective pulmonary vasodilator currently available is inhaled nitric oxide (iNO).

Data have also suggested that concomitant use of a tricuspid DeVega annuloplasty may help preserve RV function post-operatively and allow for lower RA pressures. Biventricular graft dysfunction can certainly occur with PGF, and it will be associated with elevated filling pressures for both ventricles, low CO, and hypotension. Isolated LV failure is rare after HT. When this occurs, CAD in the donor heart should be ruled out, and if needed, coronary artery bypass grafting (CABG) performed.

Other Cardiac Abnormalities

Tricuspid Regurgitation

Tricuspid regurgitation (TR) is the most common valvular abnormality after orthotopic HT. Its reported incidence varies between 19% and 84%, depending on the definition of significant TR, time of diagnosis, and the surgical transplantation technique. The incidence and severity of TR may increase over time and progression to significant TR has been associated with increased morbidity and mortality. Although the majority of patients do well with medical therapy, a small proportion eventually requires surgical intervention. The TR occurring in the early peri-operative period is, for the most part, functional. The regurgitant jet is typically central and caused by geometric distortion of the AV annular ring and dilation, and malcoaptation of the valve leaflets. Causes include bialtral anastomoses, allograft rejection with RV dysfunction, or mismatch between donor heart and recipient atrial size. In 166 patients undergoing HT with a modified bialtral surgical technique, patients without TR (67%) had a donor to recipient (D/R) ratio of < 1, whereas those with moderate to severe TR had a D/R ratio of > 1. Compared to 88 patients with the bicaaval approach, 161 recipients of the bialtral technique had an increased occurrence and progression of TR (15% at 1 month, 30% at 24 months vs. 41% at 1 month, 52% at 24 months). This lends strong support to the belief that preservation of atrial and tricuspid annulus geometry is crucial in preventing development of significant TR.

Other factors influencing atrial remodeling and enlargement, including allograft rejection > ISHLT Grade 2 and pre-operative pulmonary hypertension independently predict early TR development. The majority of patients with moderate to severe TR are asymptomatic. However, adverse clinical consequences have been reported, such as progressive RV dysfunction and failure with debilitating symptoms of dyspnea and peripheral edema, use of high diuretic doses, deteriorating functional status, renal dysfunction, and even decreased survival. The effects of sub-clinical TR remain controversial. One report described a benign clinical course for HT recipients with less than moderate TR. In contrast, Burgess et al observed that 9% of patients with TR diagnosed during the fourth post-operative week had a 90% chance of developing RV failure at a mean follow-up period of 5 years, leading to an increased mortality (28% vs. 20%, p < 0.001). Progressive RV cavity enlargement, with disproportionate elongation of the mid-minor axis, elevated right-side pressures and more advanced functional class, was associated with more severe TR. Up to 76% of patients with TR had overt right-heart failure in the immediate post-operative period, and this correlated with pulmonary hypertension after HT. Lewen et al found that 13 of 14 (93%) patients with moderate to severe TR after HT had RV volume overload and higher PVR. Williams et al noted higher RAP (mean 10 vs. 6 mm Hg, p < 0.05), lower CI (mean 2.0 vs. 2.5 L/min/m², p < 0.05) and greater right-side cardiac dimensions in 23 of 72 patients with moderate to severe TR.

With longer follow-up duration, the severity and clinical impact of TR worsens. Among 238 patients who survived ≥ 1 year after HT, Aziz et al observed persistent higher mean RAP, PA systolic pressure and RV dimensions among patients with clinical TR. Clinically, 35% of patients complained of fatigue, 61% had chronic fluid overload, 78% had lower extremity edema, and 29% had liver congestion. Furthermore, renal function and physical capacity were inferior in the same group. Progression of TR has also been correlated with change in RV diastolic area and tricuspid annulus, and intra-
operative TR severity showed a strong correlation with RV dysfunction, peri-operative mortality and odds of late survival.\textsuperscript{112, 120, 121}

The mainstay of therapy for symptomatic severe TR is use of diuretics. In refractory cases, surgical intervention with tricuspid valve annuloplasty, repair or replacement, should be considered, depending on the anatomic abnormality of the tricuspid valve apparatus. In tricuspid annular dilation, application of an annuloplasty ring may be sufficient to reduce the effective regurgitant orifice. In contrast, surgical repair or replacement is required with leaflet or chordal damage to restore a functional AV valve apparatus in the right heart. Overall, various reports have cited tricuspid valve replacement (TVR) incidence rates between 4% and 6% in HT recipients, with a mean lag time of 12 to 21 months.\textsuperscript{112, 122, 123} In another series, however, only 5/526 (0.95%) HT recipients later required tricuspid valve surgery due to severe TR.\textsuperscript{124} If replacement is performed, the best results are achieved before RV function deteriorates due to severe TR.\textsuperscript{125} Most patients have shown a reduction in their furosemide dose and lower serum creatinine levels, as well as significantly improved albumin and total bilirubin values, implying relief of hepatic congestion.\textsuperscript{112, 123} Prophylactic tricuspid valve annuloplasty (TVA) on the donor heart at the time of transplantation has been shown to reduce TR immediately after HT as well as on long-term follow-up. Sixty patients undergoing orthotopic HT with bivacal anastomosis were randomized to either concomitant DeVega TVA or no intervention on the donor’s TV. At 5 years of follow up, compared to patients without TV intervention, recipients of the DeVega TVA had lower peri-operative cardiac mortality [3 (10%) vs. 7 (23%); p < 0.05], average amount of TR (0.5± 0.4 vs. 1.5± 1.3; p < 0.05), percentage of patients with TR ≥ 2+ (0 vs. 34%; p < 0.05), serum creatinine (sCr) (1.8±0.7 vs. 2.9±2.0 mg/dL; p < 0.05) and change in sCr from baseline (0.7±0.8 vs. 2.0 ± 2.1 mg/dL; p < 0.05).\textsuperscript{111} These benefits did not result in significant differences between groups in 5 year survival. Other studies yielded similar results.\textsuperscript{126}

**Mitral Regurgitation**

Mitral regurgitation (MR) can occur in > 50% of all HT recipients in the peri-operative period.\textsuperscript{118, 127} It typically occurs in the absence of donor heart structural pathology, but in some cases it results from incomplete mitral leaflet coaptation due to atrial enlargement.

Other less common causes of MR include asynchronous atrial contraction due to donor and recipient sinus node discharge, papillary muscle ischemia, or LV outflow obstruction. In most cases, MR is mild and asymptomatic.\textsuperscript{68-71, 128-131} The need for mitral valve repair or replacement is very rare.

**Recommendations on the Management of Perioperative Tricuspid Valve Regurgitation**\textsuperscript{111, 112}:

**Class I:**

1. Tricuspid valve regurgitation identified intra-operatively and estimated to be moderate or severe (> 2+), should be re-evaluated by TTE or TEE within 24 hours of HT and closely monitored for the first few post-operative days. The frequency of subsequent follow up should be guided by clinical and hemodynamic variables.

**Level of Evidence: C.**

**Class II:**

1. DeVega annuloplasty of the donor TV can be considered to maintain the normal size of the TV annulus.

**Level of Evidence: C.**

**Pericardial Effusion**

The development of pericardial effusion has been shown to occur in more than 20% of HT recipients.\textsuperscript{132} Nonetheless, pericardial effusions are rarely associated with hemodynamic instability and typically resolve spontaneously by the fourth post-operative week.\textsuperscript{133, 134} Moreover, it is uncommon for pericardial effusions to progress to cardiac tamponade.\textsuperscript{135} In fact, large but slowly accumulating pericardial effusions usually cause little hemodynamic impairment in HT recipients. However, the development of a loculated hematoma or mediastinal bleeding, which can develop rapidly in the early post-operative period, may result in tamponade physiology.\textsuperscript{136} Occasionally, there is isolated RV tamponade that may be difficult to distinguish from primary RV failure. Echocardiography is important for recognition and timely return to the operating room for exploration and evacuation of the hematoma to improve RV mechanics and function. Although early reports identified an association between acute heart allograft rejection and the development or rapid increase of post-operative pericardial effusions, this finding was not confirmed in newer retrospective studies.\textsuperscript{132}

In a recent retrospective analysis of 203 HT recipients, the three factors that predicted the development of post-operative pericardial effusion were absence of a previous cardiac surgery, the intra-operative use of aminocaproic acid, and lower recipient weight. The reasons for the association of these factors with pericardial effusions occurring after heart transplant remain unclear.\textsuperscript{137}
Recommendations on the Management of Peri-operative Pericardial Effusions\textsuperscript{132, 137}:

\textit{Class I}:
1. Pericardial effusions occurring after HT should be monitored by echocardiogram.
2. Percutaneous or surgical drainage should be done when the pericardial effusion causes hemodynamic compromise.

\textbf{Level of Evidence: C.}

\textit{Class IIa}:
1. Pericardial effusions that are not hemodynamically compromising do not require drainage unless there is a strong suspicion of an infectious etiology.

\textbf{Level of Evidence: C.}

Pharmacologic Management of Primary Graft Failure and Right Ventricular Dysfunction

The pharmacologic management of PGF and RV heart allograft dysfunction includes the use of high-dose inotropic agents and/or pulmonary vasodilators.

\textbf{Intravenous Vasoactive Medications}

Vasoactive medications are selectively employed in the immediate post-operative period (including the period leading to separation from CPB) to achieve several specific goals: (1) inotropic support of the RV and/or LV; (2) chronotropic support; (3) increase of pulmonary blood flow/pulmonary vasodilation; and (4) peripheral arterial vasodilation or vasoconstriction.

Frequently, agents are chosen for their ability to increase both contractility and heart rate while decreasing pulmonary and systemic vascular resistance. As a potent chronotrope, inotrope, and vasodilator, isoproterenol is in many respects the ideal agent for hemodynamic support after HT, particularly in the setting of bradycardia or sinus node dysfunction. It has been a commonly used agent since the early days of HT.\textsuperscript{78} However, tachycardia can limit its usefulness, particularly in bicaval and total HT, where the incidence of sinus node dysfunction is lower than with the biatrial surgical technique. Whereas the dose range for isoproterenol is usually 2 to 10 µg/min, this drug can be titrated to achieve a target heart rate of 90 to 110 bpm. Atrial pacing combined with dobutamine achieves results similar to those of isoproterenol.

Combined infusion of low-dose dobutamine and dopamine (both at starting doses of 2.5-5 µg/kg/min) is another commonly used inotropic regimen after HT.\textsuperscript{138} This combination of inotropes may be titrated to achieve the desired hemodynamic effects. Milrinone, a phosphodiesterase inhibitor with inotropic and vasodilatory properties, may also be considered for hemodynamic support, particularly in the setting of pulmonary vascular hypertension, high systemic vasomotor tone or if there is evidence of heart allograft dysfunction upon separation from CPB.\textsuperscript{139}

In some instances, peripheral arteriolar vasoconstrictors may be required to counteract the vasodilation seen during or after CPB and maintain a systemic arterial pressure adequate for the perfusion of vital organs. While the etiology of this vasodilation is unclear, several hypotheses invoked to explain its occurrence include the release during CPB of cytokines, which may produce a systemic inflammatory response syndrome (SIRS), the effects of pre-operative medications such as angiotensin-converting enzyme inhibitor (ACEI), or relative/absolute deficiency of vasopressin. Septic shock arising from an occult intra-abdominal catastrophe must also be considered, especially if there is lactic acidosis that persists beyond 6 hours after HT.\textsuperscript{140} The range of vasodilation seen in the post-operative period ranges from mild and responsive to the infusion of a low dose of a single α-adrenergic agent to quite profound and refractory to high levels of multiple vasoconstrictors. The guanylate cyclase inhibitor methylene blue has been successfully used for the treatment of catecholamine-refractory vasoplegia after CPB.\textsuperscript{141} It has been demonstrated that an infusion of low-dose arginine vasopressin can improve vasomotor tone (and thus arterial pressure) and permit reduction or discontinuation of high-dose catecholamines in patients receiving left VADs.\textsuperscript{142} Arginine vasopressin has also been shown to prevent hypotension after CPB in patients undergoing CABG or valve surgery (Table 2).\textsuperscript{143}

Recommendations for Peri-operative Vasoactive Drugs Use in Heart Transplant Recipients\textsuperscript{139, 141-150}:

\textit{(See Table 2)}

\textbf{Class I}:
1. Continuous infusion of an inotropic agent should be used to maintain hemodynamic stability post-operatively. Inotropes should be weaned as tolerated over the first 3 to 5 days. The lowest effective dose should be used.

\textbf{Level of Evidence: C.}

2. The following therapies are suggested:
   a. isoproterenol 1 to 10 µg/min OR
   b. dobutamine 1 to 10 µg/kg/min ± dopamine 1 to 10 µg/kg/min OR
   c. isoproterenol 1 to 10 µg/min ± dopamine 1 to 10 µg/kg/min OR
   d. milrinone 0.375 to 0.75 µg/kg/min

\textbf{Level of Evidence: C.}
Table 2  Properties of Intravenous Vasoactive Drugs Used Post cardiac Transplant

<table>
<thead>
<tr>
<th></th>
<th>Peripheral vasoconstriction</th>
<th>Cardiac contractility</th>
<th>Peripheral vasodilation</th>
<th>Chronotropic effect</th>
<th>Arrhythmia risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoproterenol</td>
<td>0</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>0</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Dopamine</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Milrinone/Enoximone</td>
<td>0</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Norepinephrine</td>
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<td>+++</td>
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<tr>
<td>Phenylepherine</td>
<td>+++</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>+++</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Adapted from Kirklin JK, et al. 150

3. Continuous infusion of α-adrenergic agonists including phenylephrine, norepinephrine or epinephrine can be used to maintain adequate mean arterial pressure.

   Level of Evidence: C.

4. Low dose vasopressin (0.03-0.1 U/min) or methylene blue can be added to α-agonist for vasodilatory shock.

   Level of Evidence: B.

Pulmonary Vasodilators

Prostanoids

The prostanoids are naturally occurring substances that produce vasodilation by inducing smooth muscle relaxation. They have short half-lives, on the order of minutes, and are potent pulmonary vasodilators. Of the prostanoids, prostaglandin E1 (PGE1) and epoprostenol or prostacyclin are given IV whereas iloprost is administered by inhalation.

Prostaglandin E1

The use of continuous infusion PGE1 for RV dysfunction due to pulmonary hypertension after HT has been described in numerous case reports. 143, 144, 151 PGE1 is metabolized in the first pass through the pulmonary circulation and, therefore, the risk of systemic arterial vasodilatation is reduced but not completely eliminated. Kieler-Jenssen, et al. compared the systemic and pulmonary vasodilating effects of PGE1 with iNO and IV prostacyclin. This increased CO more than either PGE1 or iNO, but iNO reduced PVR more and was the only pulmonary selective vasodilator and thus preferred in the setting of systemic hypotension. 89, 152

Prostacyclin

Intravenous prostacyclin (PGI2) is an approved therapy for pulmonary arterial hypertension (World Health Organization Group I). Pascual et al. reported a series of 9 patients who developed RV dysfunction early after HT despite inotropic and vasodilator infusions. Prostacyclin infusion, started at 0.5 ng/kg/min and titrated to 5.0 ng/kg/min, resulted in an increased CI with reduced RAP and mean PA pressures. Therapy was maintained for 48 hours and weaned over 24 hours. 145 Comparative studies have shown more pulmonary vasodilator effects and more pronounced peripheral vasodilation with PGI2 than with nitroprusside and nitroglycerine. 89

Continuous inhaled PGI2 has also been used in the treatment of RV dysfunction after HT and cardiac surgery. Haraldsson, et al. reported its use in 9 patients (2 of whom were HT recipients) with pulmonary hypertension and an increased PVR. Inhalation of PGI2, at 10 µg/mL, produced reductions in mean pulmonary artery pressure and PVR without affecting systemic vascular resistance. No change in CO was noted. 153 The use of the intermittently inhaled prostacyclin analogue, iloprost, has also been reported. 146

Inhaled Nitric Oxide

Nitric oxide (iNO), also previously known as endothelial-derived relaxation factor, causes vasodilation by activating guanylate cyclase and increasing the production of cyclic guanosine monophosphate (cGMP), which then activates a cGMP protein kinase leading to smooth muscle relaxation. When inhaled in doses up to 80 ppm, it causes selective pulmonary vasodilation leading to reduced PVR, increased pulmonary blood flow, and reduced RV afterload. It reacts readily with oxyhemoglobin to yield methemoglobin and nitrate, thus, its activity outside the pulmonary vasculature is limited and, generally, systemic vasodilation does not occur. Nitric oxide has been shown to reduce PVR, increase RV stroke work, and reduce the incidence of RV dysfunction. It also appears to be safe with a very low incidence of methemoglobinemia with proper monitoring. In addition, because iNO produces vasodilation in the areas of the lung that are well ventilated, theoretically it should not exacerbate
ventilation/perfusion (V/Q) mismatching. Consequently, it would seem to be the optimal selective pulmonary vasodilator.154

However, despite its theoretical advantages, the clinical use of iNO remains somewhat controversial. In the United States, its only Food and Drug Administration (FDA) approved indication is for hypoxic respiratory failure in the newborn. Studies in adult respiratory distress syndrome have identified no consistent benefit. Its use in managing RV dysfunction after left VAD implantation has been described.155 Data in HT is limited to small case series and anecdotal reports.89, 147, 148, 156, 157 There have been no adequately powered trials to critically assess mortality or other outcomes.

Sildenafil
Sildenafil, a phosphodiesterase type 5 inhibitor, is an evolving therapy for pulmonary arterial hypertension that may have a role in the treatment of RV dysfunction after HT. Michelakis et al. demonstrated in 13 patients referred for heart and lung transplantation that a single dose of sildenafil was as effective and selective as iNO for pulmonary vasodilation.158 Case reports and small anecdotal studies suggest sildenafil may attenuate the rebound pulmonary hypertension sometimes noted with withdrawal of iNO and reduce PA pressure after cardiac surgery.159-161 In a series of 13 patients with RV dysfunction and low CO despite therapy with dobutamine, isoproterenol, PGE1, and iNO during the first post-operative day (1-18 hours) after HT, oral sildenafil at 3 mg/kg to a maximum of 250 mg/day resulted in immediate hemodynamic improvement.149 Although an oral form is widely available, an IV formulation is currently being evaluated in clinical trials.

**Recommendations for the Medical Management of Right Ventricular Dysfunction and Pulmonary Vascular Hypertension after Heart Transplantation**139, 141-149, 162

(See Figure 1)

**Class I:**
1. Inotropic agents that can be used to augment RV function include isoproterenol, milrinone, enoximone, dobutamine and epinephrine.

   **Level of Evidence: C.**

**Class IIa:**
1. Systemic vasodilators with pulmonary vasodilating properties including nitroglycerine and sodium nitroprusside can be used in the absence of systemic hypotension.

   **Level of Evidence: C.**

2. Selective pulmonary vasodilators that can be used in the management of peri-operative RV dysfunction include:
   (1) prostaglandins [prostaglandin E1 (alprostadil), prostaglandin I2 (epoprostenol or prostacyclin), inhaled iloprost,]; (2) inhaled nitric oxide; and 3) sildenafil.

   **Level of Evidence: C.**

**Mechanical Circulatory Support**
The use of MCS for PGF has its origin in the use of MCS for postcardiotomy shock since the 1960s.163 Most if not all VADs have been used, from extracorporeal membrane oxygenation (ECMO) circuits, to axial flow pumps, centrifugal pumps and pulsatile devices, with a small literature dominated by case series.

IABP is the least invasive form of MCS and is used as the first option for PGF after pharmacologic means.163 In most reports of MCS and PGF, there is concurrent use of IABP and other devices. Use of IABP alone is up to 66% to 70% in some reports,101, 103 with use of other VADs of 22% to 29% and ECMO in 7% to 10% of patients.

ECMO has been used to support patients with PGF who fail to wean from CPB. Some recommend ECMO as the first line of support because it makes separation from CPB possible.102, 171 However, more recent publications have not agreed with this recommendation.

Ventricular assist devices that have been used for recovery in PGF include Pierce-Donachy VAD,167 Delphin centrifugal VAD,168 ABIOMED 5000 BVs,82, 96, 166, 169, 170 Bio-medicus centrifugal pump,82, 85, 101, 164-166 Novacor,83 Thoratec,82, 83, 101, 166 HeartMate LVAD,96 and Levitronix.84, 173 Newer percutaneous devices such as the TandemHeart have anecdotally been used for PGF. In rare circumstances, a Thoratec device can be implanted as an right VAD to allow for patient physical therapy and ambulation while waiting for graft recovery. Although the choice of device is influenced by anatomical considerations, hemodynamic stability, and surgeon preferences, VADs suited for temporary circulatory support should be preferred. The VAD for PGF should be easy to prime, implant, manage, and remove. In addition, it should be less expensive than devices designed for long-term support and require little anticoagulation for the first 24 hours postoperatively. With the advances in MCS technology, the smaller devices can now provide substantial support, with less cost and less physical manipulation of the transplanted heart. The Levitronix Centrimag is a magnetically levitated centrifugal extra-corporeal pump that can provide flows of 5 to 7 L/min, and can be used for left, right, and bi-ventricular support.173 The TandemHeart is an extracorporeal axial flow
pump that has been used support cardiac function in postcardiotomy shock. Flows of 4 L/min can be maintained, and these VADs can also be used to support the LV, RV or both. Oxygenators can be inserted into the circuit of these VADs, if needed, which decreases the appeal for ECMO in adults. An IABP can be used concurrently with a VAD for PGF to facilitate afterload reduction and to maintain some pulsatile flows. The Impella Recover LD/LP 5.0 has also been used to support patients with postcardiotomy shock.

### Acute Right Ventricular Failure

<table>
<thead>
<tr>
<th>Preload Optimization</th>
<th>Hemodynamically Unstable (low output syndrome)</th>
<th>Maintenance of SR and AV synchrony</th>
<th>Ventilatory Support</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume Overload State</td>
<td>Mild progressive diuresis goal: 0.5-1 L daily negative</td>
<td>Acute RVMI or PE or Hypovolemic State (Consider 300-600 ml crystalloid challenge. (D/C if unresponsive)</td>
<td>Avoid: Inspiratory pressure &gt; 30 mmHg Auto PEEP Hypercapnia Acidosis Hypoxemia</td>
</tr>
<tr>
<td>Consider CVVH or Ultrafiltration</td>
<td></td>
<td>Cardioversion Pacemaker Implantation (atrio-ventricular) Antiarrhythmics as required</td>
<td></td>
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<tr>
<td>Minimize transfusions</td>
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</tbody>
</table>

**Inotrope-Vasopressor**

<table>
<thead>
<tr>
<th>Preferred Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobutamine</td>
</tr>
<tr>
<td>Milrinone</td>
</tr>
<tr>
<td>Dopamine</td>
</tr>
<tr>
<td>Norepinephrine</td>
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<tr>
<td>Phentolamine</td>
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<tr>
<td>Vasopressin</td>
</tr>
<tr>
<td>Epinephrine</td>
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<tr>
<td>Combinations</td>
</tr>
</tbody>
</table>

**Also consider**

- Nitric oxide trial (inhaled) or prostanooids
- Atrial septostomy
- RV assist device
- ECMO

**Figure 1** Management of right ventricular dysfunction. AV, atrioventricular; CVVH, continuous venovenous hemofiltration; MI, myocardial infarction; PE, pulmonary embolism; PEEP, positive end-expiratory pressure; SR, sinus rhythm. Adapted from Hannaf F et al.

Because of immunosuppression and the risks of infection, the shortest possible duration of support is preferred. However, once a VAD is implanted, it is often best to delay weaning attempts for 36 to 48 hours. Evidence of heart allograft recovery can be seen on TTE, although often TEE is needed because of poor transthoracic acoustic windows. Decreased requirement for inotropic support also signifies graft recovery. Hemodynamic parameters such as a decrease in RAP or RV end diastolic pressure may be helpful, but this will depend on the configuration of MCS. Increased pulse-wave amplitude on arterial waveforms can also be a sign of graft recovery.

Survival with PGF has improved over the past 15 years. Coupled with the recognition that early retransplantation within 6 months of primary HT is associated with poorer survival, there is now increasing consensus that bridging to recovery results in better survival. Patient survival rates to hospital discharge after MCS for PGF ranges from 0% to 71% depending on the report and the type of MCS used. However, these data are based on small case series or case reports. Causes of death include sepsis, hemorrhage, neurologic complications, or multisystem organ failure, specifically renal failure, and liver failure associated with RV failure.
Recommendations on the Peri-operative Use of Mechanical Circulatory Support after Heart Transplantation\textsuperscript{163, 164, 166, 168, 169}.

Class I:
1. MCS should be initiated early if there is failure to wean from CPB or other evidence of heart allograft failure such as the requirement for multiple high-dose inotropic agents to permit separation from CPB.
   
   Level of Evidence: B.

2. MCS should be considered if there is continued or worsening hemodynamic instability, such as decreasing CI and a falling MVO\textsubscript{2} or MVO\textsubscript{2} < 50% that is not corrected by appropriate resuscitation.
   
   Level of Evidence: B.

3. Support for either LV or RV failure should escalate from pharmacotherapy, to IABP, to MCS.
   
   Level of Evidence: B.

4. Small VADs such as the TandemHeart and Levitronix Centrimag can provide adequate support for RV, LV or biventricular failure, and have benefits of ease of implantation, management, and explant.
   
   Level of Evidence: C.

Class IIa:
1. In the presence of hemodynamic instability, cardiac tamponade should be excluded by direct surgical exploration. The presence of hyperacute/antibody mediated rejection should also be excluded. If hemodynamic instability persists in the absence of cardiac tamponade MCS should be considered.
   
   Level of Evidence: C.

2. The timing MCS discontinuation should be guided by evidence of graft recovery. If there is no evidence of graft functional recovery within 3 to 4 days, hyperacute and antibody mediated rejection should be excluded and the option of listing for repeat HT may be considered.
   
   Level of Evidence: C.

Class IIb:
1. Use of ECMO support in adults requires consideration of the risk of infection, immobility, and need for anticoagulation.
   
   Level of Evidence: C.

Pediatric Considerations

In the setting of acute RV failure in the peri-operative period, it is imperative that any potential residual anatomic lesions be investigated and rectified if present. This is especially important in the child with complex congenital heart disease who has undergone pulmonary artery reconstruction. The associated abnormalities may be amenable to intervention in the cardiac catheterization laboratory. Less commonly, the size of the left atrial anastomosis may be a problem. If stenosis is hemodynamically significant and not recognized intra-operatively by TEE, it is likely to cause hemodynamic instability in the immediate post-operative period and require a return to the operating room for revision. Rarely, progressive pulmonary vein stenosis can be a problem.

The complication of high PVR leading to acute RV failure, and the principles of post-operative management are similar in children and adults. However, in the literature, with studies showing variable outcomes with varying levels of PVR or transpulmonary gradient elevation\textsuperscript{179-184} have been reported and there is no consensus regarding relative or absolute cutoff values for HT candidacy. Even the values of parameters (PVR, PVR indexed (PVRi), systolic PA pressure, and TPG) whose pre-operative measurement is deemed important for risk stratification remain controversial.\textsuperscript{88, 183, 184} Responses of pulmonary arterial hypertension to vasodilators are also felt to be of variable significance in terms of an accurate prediction of outcomes.\textsuperscript{184} In addition, determination of PVR is difficult, especially in infants with complex congenital heart disease.\textsuperscript{185, 186}

In an early pediatric series of 6 patients with resting PVR values between 7 and 15 Wood Units,\textsuperscript{187} 5 underwent HT after demonstration of a decrease in PVR in response to IV nitroprusside and 4 were long-term survivors.\textsuperscript{187} Correlation of PVR and PVRi values with outcomes after HT in 82 patients aged 4 to 61 years showed\textsuperscript{188} that 33% of patients with a PVRi of > 6 Wood Units developed RV failure with a mortality of 15%, whereas no patient with a PVRi below this value developed RV failure. The results also confirm that high PVR is not an absolute contraindication to HT as 28 of 33 patients with a PVRi of > 6 Wood Units and 10 of 12 patients with a PVRi of > 9 Wood Units were successfully transplanted.

The infant population with either congenital heart disease predisposing to systemic pulmonary vascular pressures (duct dependent single ventricle physiology) or cardiomyopathy have a low incidence of significant post-operative complications due to pulmonary vascular hypertension. Of 139 consecutive infant HT recipients up to 12 months of age, only 1 death occurred as a result of pulmonary vascular hypertension.\textsuperscript{189}
Recommendations for the Management of Early Heart Allograft Dysfunction in Pediatric Recipients:179, 181, 183-187, 189:

**Class IIb:**
1. The increased risk of post-operative RV dysfunction must be carefully evaluated in children, although evidence suggests that children can safely undergo HT despite elevation of PVR above values considered unsafe in adults.
   
   **Level of Evidence: C.**
2. Contrary to the experience and practice in adults, the first choice for support in the setting of PGF in the pediatric setting should be ECMO.
   
   **Class IIa, Level of Evidence C.**

**Arrhythmias**

Heart rate is variable and ranges from bradycardia to tachycardia. Factors such as parasympathetic denervation, surgical trauma, catecholamine administration, and even genomic variations in the β-adrenergic receptor may affect the sinus node rate.94

**Bradycardia**

Most HT recipients display normal sinus rhythm upon reperfusion. A complete or incomplete right bundle branch block may be present in 14% to 60% of patients.190, 191 PR and QT intervals remain normal, despite the bundle branch block. However, the incidence of bradycardia ranges from 8% to 64%.192-194 Sinus node dysfunction in the immediate post-operative period may be related to surgical trauma, sinus node ischemia, and recipient medical therapy and donor age and ischemic time.195 In addition, the donor heart has an increased sensitivity to and production of adenosine, which may contribute to some peri-operative bradycardia.196, 197 Absolute or relative bradycardia typically occurs within the first 2 weeks.198

Rates of sinus node dysfunction and the need for permanent pacing have decreased with the adoption of the bicaval Wythenshawe technique, and the total heart technique that has separate anastomoses of the pulmonary and caval veins, to replace the standard biatrial technique pioneered by Lower and Shumway.192, 196, 199 In a randomized study of surgical techniques, 36 of 41 patients with the bicaval approach had sinus rhythm in the operating room, with the rest returning to sinus rhythm in a few days. In contrast, the biatrial method resulted in only 20 of 40 patients with spontaneous sinus rhythm and 5 patients in whom sinus rhythm never returned.200 In another report the rate of temporary pacing was up to 38% in the standard biatrial approach to transplantation and only 20% with the bicaval technique.201 More recent data suggest that hospital length of stay and need for pacing are also lower with the bicaval technique.202

With modern surgical techniques, 18% to 27% of HT recipients require temporary pacing.194, 203 Sinus node depression is usually corrected by chronotropic support with isoproterenol, dobutamine, or dopamine, which are routinely used (see section on Pharmacologic management post-transplant). Other pharmacologic agents that have been used for bradycardia after HT are theophylline and terbutaline. As there is invariably some diastolic dysfunction and a reduced stroke volume in the post transplant heart, maintaining heart rate is crucial to maintaining CO.

**Tachyarrhythmias**

Sinus tachycardia is the most common heart rhythm after HT. With loss of vagal innervation and parasympathetic input, the transplanted heart will assume the automatic sinus rate, which should be < 130 bpm. However, both ventricular and atrial tachyarrhythmias may occur in the post-operative period.

Atrial fibrillation (AF) and atrial flutter (AFL) are common in the post-operative period. Studies have suggested an incidence of 7% to 25% for arrhythmias lasting longer than 1 hour or leading to hemodynamic compromise.190, 204-206 Within the first 2 weeks after HT, AF is more common than AFL, occurring in 5% to 24% of patients, although more contemporary estimates are lower (6%-10%). The incidence of AF after HT, may be less than that occurring after conventional cardiac surgery.190, 207 When AF occurs within 2 weeks of transplantation, it does not appear to be associated with rejection.204, 206 In contrast, later AF may be associated with rejection and an increase in overall mortality.208 The likelihood of AF after HT is greater with older donor and recipient age. The incidence of AF in the post-operative period does not appear to be affected by the surgical technique. A large retrospective study showed that bicaval and total HT are associated with a lower incidence of AFL201, 206 due to the physical reduction of left atrial size by these procedures. The development of atrial tachyarrhythmias may also be due to conduction abnormalities in the donor heart. Accessory pathways and re-entrant circuits have been described, in addition to standard AFL macro-reentrant circuits. These can be treated with radio-frequency ablation.207 Although adenosine administration can help to clarify the diagnosis of atrial arrhythmias in the HT recipient, the dose should be reduced by one-half to one-third 209 because of an increased sensitivity to its effects. Premature ventricular contractions
can be seen in as many as 95% of HT recipients in the immediate post-operative period. Non-sustained ventricular tachycardia (VT) occurs in less than 2% of HT recipients, and it is triggered by increased sensitivity to catecholamines and longer ischemic times.

Pharmacologic management of tachyarrhythmias is limited because the donor heart is denervated. Digoxin will not be effective for rate control. β-blocker therapy can lower heart rates through direct effect on cardiac β receptors. The non-dihydropyridine calcium channel blockers, verapamil and diltiazem, can help control heart rate, but should be used judiciously because they can have negative inotropic effects and inhibit the metabolism of CNI. Amiodarone can safely be used after HT for atrial and ventricular arrhythmias. Sotalol can be used in patients without significant renal dysfunction. Dofetilide has many drug interactions and should be avoided if possible unless there are no other antiarrhythmic options for rate control.

**Recommendations for the Peri-operative Management of Cardiac Arrhythmias in Heart Transplant Recipients**

**Class I:**

1. Pharmacologic chronotropic agents, including isoproterenol and theophylline can be used in the perioperative setting to increase heart rate.

   **Level of Evidence: B.**

2. Atrial and ventricular temporary epicardial pacing wires should be placed at the time of HT even if the initial rhythm is sinus.

   **Level of Evidence: B.**

3. After HT temporary pacing should be initiated in the setting of relative bradycardia to maintain heart rates of > 90 bpm.

   **Level of Evidence: B.**

4. Pacing guidelines of the American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS) and the European Society of Cardiology (ESC) lack recommendations specific for temporary pacing early after HT. Recommendations for permanent pacing exist for inappropriate chronotropic response 3 weeks after HT. Standard atrium-paced, atrium-sensed, inhibited-rate modulation (AAIR) or dual-paced, dual-sensed, dual-response to sensing, rate modulation (DDDR) pacemakers are preferable.

   **Level of Evidence: C.**

5. Treatment of tachyarrhythmias should be aimed at rate control.

   **Level of Evidence: B.**

6. Persistent tachyarrhythmias, whether atrial or ventricular, should prompt investigation of possible rejection and electrophysiological evaluation if rejection is absent.

   **Level of Evidence: B.**

7. Sustained VT should be evaluated with both an angiogram and an endomyocardial biopsy (EMB).

   **Level of Evidence: B.**

**Class IIa:**

1. The Class III antiarrhythmics sotalol and amiodarone can be safely used in HT recipients and have minimal interaction with immunosuppressive agents.

   **Level of Evidence: C.**

2. Non-dihydropyridine calcium channel blockers and beta-blockers may be used in HT recipients for rate control.

   **Level of Evidence: B.**

**Renal Function and Fluid Status Management**

There are many insults to the kidneys in HT recipients. The renal function of many chronic heart failure patients is impaired due to chronic low output states, high venous filling pressures, and upregulation of the renin-aldosterone-angiotensin system leading to salt and water retention. Volume overload persisting after donor HT can acutely distend the more sensitive, ischemically injured, pressure overloaded RV and aggravate post-operative RV dysfunction.

Cardiac cachexia and hypoalbuminemia can result in low plasma oncotic pressures, ascites, peripheral edema, and poorer outcomes. The cardiorenal syndrome and diuretic resistance typical of advanced heart failure complicates post-operative management of HT recipients. Early institution of CNI can further reduce responsiveness to diuretics due to the renal vasoconstrictive properties of these drugs.

Patients receiving successful MCS can be better nourished and euvoletic to even mildly hypovolemic at the time of HT. The end-organ sequelae of chronic heart failure are often resolved in these patients. Whereas renal function and nutritional status are improved, the risk of peri-operative bleeding and resulting hypovolemia may be increased.

The use of blood products and management of coagulopathy in HT recipients is discussed elsewhere in these guidelines.
After HT, renal function may be a marker of cardiac function. As RAP rise above 15 to 20 mm Hg, there is increased renal venous pressure and decreased perfusion pressure.\textsuperscript{213-215} Perfusionists can perform ultrafiltration during CPB to reduce volume overload. Adequate CO can be maintained using pharmacologic support or MCS if needed. If oliguria develops, loop diuretics can be used. If urine output is < 1 mL/kg/min, appropriate interventions should be initiated. If preload is low, with RAP < 10 to 12 mm Hg, volume replacement should be considered. If the RAP is high, then continued use of diuretics or ultrafiltration should be considered to reduce renal preload and improve renal function.\textsuperscript{216, 217} In the heart failure and cardiorenal literature, volume overload has been recognized as a risk factor for worsening renal function.\textsuperscript{218, 219} Ultrafiltration can be performed with either standard dialysis platforms, or with the smaller continuous ultrafiltration machines. The smaller machines can provide substantial rates of ultrafiltration with limited effect on the mean arterial pressure, and do not require the placement of dialysis catheters.\textsuperscript{220}

The incidence of renal failure requiring hemodialysis after HT ranges from 1% to 15%\textsuperscript{217, 221-224} and is associated with increased mortality up to 50% compared with 1.4% to 4.2% in patients not requiring renal replacement therapy.\textsuperscript{211, 222, 223} The use of dialysis in the immediate post-transplant setting can be transient.\textsuperscript{223} Risk factors for the development of renal failure are longer bypass time, diabetes mellitus, and low serum albumin levels, but not pre-operative sCr.\textsuperscript{223}

For patients requiring MCS, ultrafiltration or dialysis can be performed into the circuit in some systems, and should be considered earlier in the setting of RV failure.\textsuperscript{169}

If renal failure occurs in the immediate post-operative period after HT, the addition of monoclonal or polyclonal antibodies to delay initiation of CNI should be considered. In 2007, 51% of HT recipients received mono- or polyclonal antibody therapy, 28% with an anti-CD 25 (IL-2) receptor antagonist, and 20% with anti-thymocyte globulin.\textsuperscript{225} The use of both anti-thymocyte globulin and the IL-2 receptor antagonist, basiliximab, to delay CNI initiation led to improved renal function early after HT.\textsuperscript{230} More recently, a single-center comparison of anti-thymocyte globulin with basiliximab suggested that induction with anti-thymocyte globulin confers better renal protection than basiliximab with sustained benefits to 6 months after HT.\textsuperscript{232} Strategies to delay the initiation of CNI, should be considered when there is pre-operative renal dysfunction, or a post-operative worsening of sCr > 0.5 mg/dL (44.2 umol/L).

### Recommendations for Peri-operative Renal Function and Fluid Status Management in Heart Transplant Recipients\textsuperscript{210, 220, 223, 232}

#### Class I:
1. The CVP should be maintained between 5 and 12 mm Hg, a level that provides adequate cardiac filling pressures without causing RV overload.

   **Level of Evidence:** C.

2. Colloid replacement is generally preferred in the first 24 hours after HT; blood, if indicated, is the first choice.

   **Level of Evidence:** C.

3. Compatible blood products may be safely administered after HT without increasing the risk for rejection. In the setting of ABO incompatible pediatric HT special care must be taken in the selection of compatible products to account for both donor and recipient blood types.

   **Level of Evidence:** B.

4. Blood products should be leukocyte-depleted. Blood products should be cytomegalovirus (CMV) negative if donor and recipient are CMV negative.

   **Level of Evidence:** B.

5. IV loop diuretics are used to decrease volume overload. In addition to intermittent IV bolus, continuous IV infusion of loop diuretics with or without sequential nephronal blockade using thiazide diuretics or aldosterone antagonists may be necessary.

   **Level of Evidence:** C.

6. Hemodialysis for renal failure should be initiated early for both volume management and renal replacement. If the recipient is anuric, oliguric, or has a sharp rise in sCr within 2 to 4 hours after HT, then hemodialysis may be necessary.

   **Level of Evidence:** B.

#### Class IIa
1. Ultrafiltration should be considered if RAP remains elevated (> 20 mm Hg) despite pharmacologic interventions.

   **Level of Evidence:** B.

#### Class IIb
1. Delay of initiation of CNI therapy should be considered if there is significant pre-operative renal insufficiency or deterioration of kidney function in the first 2 post-operative days.

   **Level of Evidence:** C.
Peri-operative and Post Operative Metabolic Issues

Management of Diabetes Mellitus and Non-diabetic Hyperglycemia

Hyperglycemia, which commonly complicates the clinical course after HT, may be due to peri-operative exacerbation of pre-existing diabetes mellitus (DM), stress-related metabolic derangements, or peri-operative corticoid (CS) therapy. Studies have shown that tight glycemic control (80-110 mg/dL) in surgical intensive care unit (ICU) patients is associated with reduced hospital mortality, bloodstream infections, acute renal failure requiring hemodialysis, and transfusion requirements. In one study continuous insulin infusions in diabetic patients undergoing CABG reduced mortality and the incidence of deep sternal wound infections. High dose CSs, such as methylprednisolone administered at the time of CPB, have been shown to exacerbate hyperglycemia and impair glycemic control in the post-operative period.

A variety of protocols have been developed for post-operative glycemic management. In addition to the goal of achieving tight glycemic control, it is also imperative to avoid dangerous hypoglycemia. In a recent trial of intensive glucose control (glucose target range 81-108 mg/dL) versus conventional control (glucose < 180 mg/dL) in 6104 medical intensive care patients found that the higher mortality rate in the intensive control was attributable to hypoglycemic events. Many protocols include a concomitant dextrose infusion to minimize this risk. Although no randomized trials support the use of one protocol over another, a review of 12 regimens has shown that while target ranges for blood glucose are variable, levels < 200 mg/dL are consistently associated with reduced surgical site infections.

Diabetics should be monitored for the development of diabetic ketoacidosis, because even Type II diabetics may develop ketosis in the setting of stress such as surgery.

As a general rule, oral hypoglycemics should be discontinued pre-operatively and not used in the immediate post-operative period as they may be associated with complications such as lactic acidosis (metformin), or fluid retention (thiazolidinediones). The oral hypoglycemics may be safely re-introduced during the first week after HT when glucose levels have become stable. Insulin-dependent diabetics should be converted back to intermittent subcutaneous insulin when it is safe to do so.

Recommendations for the Peri-operative Management of Hyperglycemia in Heart Transplant Recipient:

Class I:
1. Oral hypoglycemic agents should be discontinued pre-operatively.
   Level Evidence: C.
Class IIa:
1. A continuous infusion insulin regimen should be used to maintain blood glucose below 200 mg/dL during the ICU stay.
   Level of Evidence: B.
2. Aggressive management of hyperglycemia should be continued for the duration of hospitalization.
   Level of Evidence: C.

Prophylaxis Against Infection in the Early Post-operative Period

Anti-infective agents are administered early after HT to prevent post-operative and opportunistic infections, and to continue treatment of pre-existing chronic infections (such as chronic VAD-related bacterial infections). Specific guidelines for the prevention and treatment of opportunistic infections will be provided in separate guidelines. It is important to recognize that antimicrobial regimens should be tailored to the pathogens prevailing in the transplant center. For example, if a hospital has a high incidence of aspergillosis in the ICU, it might be appropriate for patients undergoing HT at that institution to receive inhaled anti-fungal agents.

Recommendations for Antibacterial Prophylaxis/Treatment:

Class I:
1. Pre-operative antibiotic prophylaxis should be employed prior to the transplant operation.
   Level of Evidence: B.
2. Drugs should be selected based upon their activity against usual skin flora, specifically staphylococcus species.
   Level of Evidence: B.
3. If a chronically infected device such as a VAD or a pacemaker is present, then peri-operative antibiotics should be selected based upon microbiologic sensitivities.
   Level of Evidence: B.
4. In the event that the donor had an ongoing bacterial infection, a course of suitable antibiotics should be considered.
   Level of Evidence: B.
Recommendations for Peri-operative Antiviral Prophylaxis in Heart Transplant Recipients:\textsuperscript{243}

(See Table 3)

<table>
<thead>
<tr>
<th>Group</th>
<th>Recommendations/Options</th>
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</table>
| D+/R- | Oral ganciclovir (1000 g PO TID) or valganciclovir (900 mg PO/day) for 3 months  
or  
IV ganciclovir (5-10 mg/kg/day) for 1-3 months  
Preemptive therapy generally not preferred due to high risk of disease  
Some HT centers will add CMV immune globulin for high risk patients |
| R+    | Oral ganciclovir (1000 g PO TID) or valganciclovir (900 mg PO/day) for 3 months  
or  
IV ganciclovir (5-10 mg/kg/day) for 1-3 months  
or  
Preemptive therapy. Monitor with nucleic acid testing or CMV antigenemia assay  
Therapy with IV ganciclovir or oral valganciclovir |

CMV, cytomegalovirus; D, donor; HT, heart transplant; IV, intravenous; PO, oral (per os); R, recipient; TID, 3 times daily.

Class I:

1. Prophylaxis against CMV should be initiated within 24 to 48 hours after HT.

   Level of Evidence: A.

2. The CMV serologic status of the donor and recipient may be used to stratify the patient as low, intermediate, or high risk for developing a CMV infection.

   Level of Evidence: A.

3. Intravenous gancyclovir may be administered to intermediate and high risk patients whereas patients at low risk for CMV infection may only receive anti-herpes simplex virus prophylaxis with acyclovir. (See Table 5.)

   Level of Evidence: A.

Recommendations for Peri-operative Anti-Fungal Prophylaxis in Heart Transplant Recipients:\textsuperscript{244}

Class I:

1. Antifungal prophylaxis to prevent mucocutaneous candidiasis should be initiated after the recipient is extubated. The agents most commonly used are nystatin (4-6 mL [400,000 to 600,000 units] 4 times daily, swish and swallow) or clotrimazole lozenges (10 mg).

   Level of Evidence: C.

Recommendations for Anti-Protozoal Prophylaxis in Heart Transplant Recipients:\textsuperscript{245}

Class I:

1. Prophylaxis against \textit{Pneumocystis jiroveci} (formerly \textit{Pneumocystis carinii}) pneumonia and \textit{Toxoplasma gondii} (in indicated cases) should also be initiated in the early post-operative period. Trimethoprim/sulfamethoxazole (80 mg TMP/160 mg SMZ, 1 single- or double-strength tablet per day) is the most commonly used medication. In the setting of a sulfa allergy or glucose-6-phosphate dehydrogenase deficiency, alternative regimens can be used, including: (1) aerosolized pentamidine (AP) isethionate (300 mg every 3–4 weeks); (2) Dapsone (diaminodiphenylsulfone) with or without TMP or pyrimethamine (50–100 mg/day). Pyrimethamine may be administered weekly (25 or 50 mg) to supplement dapsone (50–100 mg/day). Dapsone is metabolized via the hepatic cytochrome P-450 system (CYP3A); (3) Atovaquone (1500 mg PO QD); (4) Clindamycin and pyrimethamine.

   Level of Evidence: B.

Peri-operative Infection Treatment and Prophylaxis in Pediatric Heart Transplant Recipients

Infectious considerations are similar in children as in adults, though with less objective evidence in the literature upon which to base guidelines or recommendations. Options as outlined within these guidelines include expectant observation, prophylactic therapy, or pre-emptive therapy. In addition, infants with an open chest and/or requiring ECMO support are a particularly high-risk group for invasive fungal infection with a mortality of nearly 50% within the Pediatric Heart Transplant Study.\textsuperscript{246} Therefore, it is common practice to use an IV anti-fungal agent such as fluconazole for prophylaxis in this group. In addition, in a large multicenter registry, \textit{Pneumocystis jiroveci} has been shown to occur at a low incidence of 1% but associated with increased mortality, primarily within the first year post-transplant.\textsuperscript{247} Therefore, it is common practice to continue prophylaxis for at least 3 months and for up to 24 months after heart transplantation.

Recommendations for Peri-operative Infection Prophylaxis and Treatment in Pediatric Heart Transplant Recipients:\textsuperscript{242-245}

Class Ib:

1. IV anti-fungal prophylaxis should be considered for infants (< 1 year of age) with an open chest and/or requiring ECMO support in the peri-operative period.

   Level of Evidence: C.
2. Prophylaxis for *Pneumocystis jiroveci* should be instituted for a minimum of 3 months up to a maximum of 24 months after HT.  

**Level of Evidence: C.**

**Topic 3: Evaluation of Allosensitization, Approaches to Sensitized Heart Transplant Candidates, Hyperacute and Delayed Antibody Mediated Rejection**

**Introduction**

Serum antibodies directed against human leukocyte antigens (HLA) have been associated with allograft rejection, dysfunction, and loss. This was first demonstrated by Patel and Terasaki, who documented poor survival of renal allografts in recipients whose serum caused lysis of donor leukocytes in an in vitro crossmatch test. This cell lysis was later proven to be due to the presence of alloantibodies in the recipient’s serum directed against donor HLA antigens. Since then, various modifications of crossmatch testing, in which recipient’s serum is combined with donor cells, have been routinely used to determine donor-recipient compatibility. The crossmatch test helps clinicians avoid transplantation of an organ into a recipient with donor specific antibodies.

**Methods for the Detection of Anti-HLA Antibodies**

The detection of anti-HLA antibodies requires the recipient’s serum as the source of “unknown” anti-HLA antibodies and cells or materials bearing “known” HLA antigens. These panel reactive antibody (PRA) tests, which determine the percentage of possible donor HLA antigens targeted by the recipient’s preformed circulating antibodies, is routinely used to assess the likelihood of a recipient to reject a donor organ (Table 4).

The target HLA antigens may be constitutively expressed antigens on the cell membranes of T-cells (Class I HLA antigens) and of B cells (Class I and II HLA antigens). Antibodies directed against these antigens may be detected in a number of ways:

1. The complement-dependent cytotoxicity (CDC) method evaluates target (donor) cell lysis occurring in the presence of antibody-antigen complex and complement activation and it is detected by the addition of a dye that penetrates only into the lysed cells. This method has been for the most part superseded by flow-cytometry techniques.

2. Complement-independent flow-cytometry enables the detection of the primary anti-HLA antibody after target (donor) cells are incubated with the recipient’s serum and a secondary fluorescent-labeled antiglobulin (AHG).

| Table 4 Panel-Reactive Antibody and Crossmatch Methods Among 20 Histocompatibility Laboratories |
|---------------------------------|---------|---------|
| Method Description | PRA (%) | XM (n) |
| CDC with T lymphocytes without AHG | 8 | 9 |
| CDC with T lymphocytes with AHG | 15 | 12 |
| CDC with B lymphocytes without AHG | 8 | 10 |
| CDC with B lymphocytes with AHG | 5 | 5 |
| Flow Cytometry with T lymphocytes | 3 | 12 |
| Flow Cytometry with B lymphocytes | 1 | 11 |
| Flow beads with Class I antigens | 7 | - |
| Flow beads with Class II antigens | 2 | - |
| ELISA with Class I antigens | 7 | |
| ELISA with Class II antigens | 5 | |

AHG, anti-human globulin; CDC, complement-dependent cytotoxicity; ELISA, enzyme-linked immunosorbent assay; n, number of programs using the indicated technique; PRA, panel-reactive antibody; XM, crossmatch methods.

Adapted from Betkowski AS, et al.

Briefly, these PRA tests consist of adding the recipient’s serum to HLA-antigen-bearing cells (lymphocytes) obtained from a panel of random individuals from the local population (usually 30-60) who are felt to be representative of the potential donor pool. The PRA result represents the percentage of the panel of cells which undergo lysis in the presence of the recipient’s serum. This PRA measurement does not specify the HLA antigens against which the recipient has antibodies; it simply estimates the percentage of the local donor pool that will be incompatible. At most transplantation centers a percent PRA ≥10% is the threshold above which virtual or real time prospective crossmatch should be done to determine if the recipient antibodies are actually directed against donor tissue (see below). The correlation between preformed antibodies directed against HLA antigens and poor outcomes after HT has been demonstrated with both cytotoxicity and flow cytometry methods. In both these cell-based assays, recipient antibodies not specific for donor HLA antigens may also bind to target cells and cause their lysis. The CDC assay requires larger amounts of blood for antibody screening than complement-independent assays, an important consideration in pediatric HT candidates.

3. Solid-phase assays permit identification of specific HLA-antibodies because individual HLA antigens are mounted...
onto an artificial support such as plastic plates for ELISA, microbeads for flow cytometry or the multiplex platform Luminex.

The common denominator of these methods is the presence of a high-affinity, clinically available anti-IgG antibody coupled with an enzyme which produces a colorimetric reaction when exposed to specific substrates (ELISA) or fluorochromes (flow cytometry).

Evaluation of antibody specificity using panels of cells can be difficult, especially in highly sensitized patients, even after cumbersome adsorption/elution techniques to remove non-HLA antibodies. Furthermore, the HLA types on the panel cells used for screening should reflect the antigenic frequency in the regional population of the transplant center. The availability of single antigen-coated plates/beads greatly facilitates the evaluation of antibody specificity. In highly sensitized recipients, these assays can provide valuable information regarding the specific HLA antigens not targeted by recipient antibodies and therefore considered acceptable donor/recipient pairs.

The availability of single-antigen assays also permits the identification of rare or infrequently expressed HLA antigens. For example, the less recognized anti-HLA class II DP alloantibodies may mediate chronic humoral rejection in renal transplant recipients. In addition, solid-phase PRA tests enable one to distinguish a positive cytotoxic result due to binding of anti-HLA antibodies to HLA antigens from cell lysis due to binding of antibodies to non-HLA molecules also expressed on the surface of T and B cells. It is important to note that solid-phase assays can be altered by various preparations containing HLA-Ab (IV Ig) or non-HLA antibodies (antiplastic-antibodies, especially in patients with hemodialysis or MCS).

Ideally more than 1 PRA screening method should be performed on more than 1 occasion (separated by at least 2 weeks) for accurate assessment of the recipient’s allosensitization status. The number of patients at risk for developing antibodies against donors’ HLA antigens is increasing due to previous transplants, use of homograft materials in cardiac surgery, exposure to paternal HLA antigens during pregnancy and transfusion of blood products. Although the use of MCS devices may be associated with elevated PRA levels, the antibodies which develop in this setting may not be directed against HLA antigens and the crossmatch may be negative. There is no universally accepted definition of a PRA threshold above which a real time or virtual prospective crossmatch should be done.

In a real-time prospective crossmatch, the donor’s lymphocytes are directly exposed to the recipient’s serum and observed for lysis prior to accepting the donor for transplant.

Real-time prospective crossmatch cannot be prospectively performed in the absence of readily available donor cells or when a short organ ischemia time is essential for successful transplantation. This is the case in HT, particularly when the donor heart is geographically distant from the recipient’s hospital. The predominant practice has been to accept only organs from local donors for immunologically sensitized HT candidates (candidates with serum antibodies directed against HLA antigens), so that a prospective donor/recipient crossmatch can be performed. The need for a prospective crossmatch limits the pool of potential donors, and thus results in longer waiting times, and higher waiting list mortality while. As described above, assays that use HLA antigen-coated solid-phase matrices are capable of identifying HLA-specific antibodies with high sensitivity and accuracy. These methods have been used to predict immune compatibility between donor and recipient by comparing the potential recipient’s HLA-specific antibodies with the HLA type of the prospective donor, an approach called the virtual crossmatch. The use of the virtual crossmatch in kidney allocation is currently being debated. Thus far, in kidney transplantation the availability of virtual crossmatch has not eliminated the need for a serologic prospective crossmatch. If this demonstrates donor/recipient incompatibility, the organ is reallocated to a different recipient.

**Recommendations for the Evaluation of Donor/Recipient Histocompatibility**:

**Class I**:
1. Screening PRA should be performed in all HT candidates. When the PRA is elevated (≥ 10%) further evaluation is recommended.
   
   **Level of Evidence: C.**

2. The specificity of circulating antibodies should be determined with a solid-phase assay such as flow-cytometry, if possible, in a regional certified HLA laboratory.
   
   **Level of Evidence: C.**

3. The complement fixation capability of detected antibodies should be reported.
   
   **Level of Evidence: C.**

4. The anti-HLA Class I and II specificities (i.e., any HLA antibody directed against HLA-A, HLA-B, HLA-Cw, HLA-DR, and HLA-DQ antigens) should be defined. In the absence of international standards, each transplant
center must define the threshold of antibody levels used to define which specific donor HLA antigens confer an unacceptable rejection risk.

Level of Evidence: C.

5. The virtual crossmatch, which compares recipient anti-HLA antibody specificities with donor HLA antigens, should be routinely used to increase the donor pool for sensitized recipients.

Level of Evidence: C.

Risk-Assessment and Prophylaxis Strategies for Allosensitized Heart Transplant Candidates

Pre-transplant Strategies for Sensitized Patients

Several therapeutic regimens have been used to reduce allosensitization before HT or to treat antibody-mediated rejection (AMR). These therapies, however, have not been tested in randomized, controlled clinical trials. The two main strategies that have been employed to reduce allosensitization include high-dose IV immunoglobulin (IV Ig) and plasmapheresis (PP) combined with IV Ig or low-dose CMV hyperimmune globulin (CMV Ig). There are several agents and interventions that can augment the potency of these treatment modalities, including splenectomy, anti-CD20 antibody therapy, and clinically available immunosuppressive modalities (Table 2).252

High-dose IV Ig

The initial mechanism of action of IV Ig may be neutralization/elimination of preformed antibodies by anti-idiotypic antibodies present in IV Ig. The IV Ig is believed to diminish circulating antibodies levels, to inhibit B-cell antibody synthesis and to attenuate complement-mediated endothelial cell injury. This treatment modality can be used to desensitize patients waiting for transplantation or used postoperatively for treatment of AMR, is easily administered and is less expensive than plasmapheresis. Treatment with IV Ig does not uniformly reduce allosensitization, requires administration of a large volume of fluid, results in a less rapid antibody removal than plasmapheresis and effectiveness varies from batch to batch. Its effectiveness has not been proven in patients with a high titer of donor specific antibodies. In addition for a period of time after IV Ig administration donor specific antibody levels must be determined with alternative methods. The IV Ig is given at a dose of 2 g/kg over 4 hours and this dose is repeated monthly 4 times.

Plasmapheresis

Plasmapheresis rapidly reduces anti-HLA or isoagglutinin antibodies levels. This reduction permits immunomodulation at a lower IV Ig dose and induces donor-specific unresponsiveness. Plasmapheresis has predictable kinetics, is effective in patients with high donor-specific antibodies titers, which can be easily monitored during therapy. The long-term effectiveness of plasmapheresis is limited by the recurrence of donor-specific antibodies if transplant does not immediately follow this desensitization therapy. Performance of plasmapheresis requires central access and the procedure is expensive.

Plasmapheresis with Low-dose CMV Ig

This procedure may be considered for patients requiring urgent transplantation both pre-and post-operatively. Each plasmapheresis session is followed by the administration of CMV Ig at a dose of 100 mg/kg. Inadequate availability of CMV Ig limits the delivery of this therapy.

Anti-CD20 (Rituximab)

The use of rituximab results in rapid and sustained ablation of the B cell compartment, but it has no effect on plasma cells or on circulating antibody levels. Rituximab inhibits CD-20+ B-cells proliferation and induces apoptosis in these cells by antibody- and complement-dependent cytotoxicity. Circulating antibodies levels may be more effectively reduced when rituximab is combined with plasmapheresis or IV Ig. Rituximab can be used pre- and postoperatively, is generally well tolerated and it associated with little toxicity. Rituximab does not eliminate plasma cells in the spleen and bone marrow, it cannot independently reduce donor-specific antibody titers, it may have immunosuppressive effects which persist for months and it is very costly. Rituximab is given at a dose of 375 mg/m² weekly for four weeks and its effects are monitored with the performance of CD-20+ cell count in the peripheral blood.260 Reconstitution of normal B cells typically begins 6 to 9 months after termination of rituximab.

Immuoabsorption

This therapy removes IgG 1, 2, and 4 subclasses, but not the complement-binding IgG3. Immunoabsorption can be carried out pre- and post-operatively and it is effective in patients with high donor-specific antibodies titers, which can be easily monitored during and after therapy. Therapy is continued until IgG and PRA levels have been significantly reduced compared to baseline. The disadvantages of immunoabsorption include a high cost and an increased risk of infections. This modality is generally not totally effective when used alone.

Splenectomy

Splenectomy, which can now be performed with minimally invasive techniques, is associated with a reduction in plasma cells and precursor B cells. It may produce more
effective antibody reduction when combined with plasmapheresis or IV Ig. The main limitations of splenectomy are its inability to independently reduce donor-specific antibodies titers and the life-long risks of sepsis from encapsulated bacteria.\textsuperscript{258}

### Table 5  Examples of Desensitization Therapies

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasmapheresis</td>
<td>(A, F) 1.5 volume exchanges</td>
<td>(A) 5 consecutive days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(B) 5 times, every other day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(C) 2-3 times/week until transplant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(D) 5 times, every other day, every 2-4 weeks</td>
</tr>
<tr>
<td>Intravenous immunoglobulin (IV Ig)</td>
<td>(A, B) 2g/kg IV divided over 2 days</td>
<td>(A) Every 2-4 weeks</td>
</tr>
<tr>
<td></td>
<td>(C) 2-3 g/kg IV divided over 4 days</td>
<td>(D) Every 2-4 weeks</td>
</tr>
<tr>
<td></td>
<td>(D) 0.1 mg/kg IV</td>
<td>(E) Every 4 weeks</td>
</tr>
<tr>
<td></td>
<td>(E) 100 mg/kg IV</td>
<td>(F) 20 g (of 10% IV Ig)</td>
</tr>
<tr>
<td></td>
<td>(G) 150 g (of 10% IV Ig) divided over 3 rounds</td>
<td>(G) Every 4 weeks</td>
</tr>
<tr>
<td>Rituximab</td>
<td>(A) 1g IV</td>
<td>(A) Weekly x 4</td>
</tr>
<tr>
<td></td>
<td>(C, E) 375 mg/m\textsuperscript{2}</td>
<td>(C) x 2 doses</td>
</tr>
<tr>
<td></td>
<td>(G) 500 mg</td>
<td>(E) Weekly x 4</td>
</tr>
<tr>
<td>Cyclophosphamide (used in the past)</td>
<td>(A) 1 mg/kg orally</td>
<td>(G) Every 2 weeks</td>
</tr>
<tr>
<td></td>
<td>(C) 0.5 mg-g/m\textsuperscript{2}</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(D) 1 mg/kg orally</td>
<td></td>
</tr>
</tbody>
</table>

(A) UCLA; (B) Stanford University; (C) University of Maryland; (D) University of Toronto; (E) University of Wisconsin; (F) Loyola University Chicago; (G) University of Berlin.

Adapted from Kobashigawa J, et al.\textsuperscript{252}

### Recommendations for the Risk-Assessment and Prophylaxis Strategies for Allosensitized Heart Transplant Candidates\textsuperscript{252, 260}:

(See Table 5)

**Class IIa:**

1. A complete patient sensitization history, including previous PRA determinations, blood transfusions, pregnancies, implant of homograft materials, previous transplantation, and use of a VAD is required to assess the risk of heart allograft AMR.

   **Level of Evidence:** C.

2. A PRA \(\geq 10\%\) indicates significant allosensitization and it should raise the question of whether therapies aimed at reducing allosensitization should be instituted to minimize the need for a prospective donor/recipient crossmatch.

   **Level of Evidence:** C.

3. The results of the retrospective donor recipient crossmatch may be considered to make decisions regarding immunosuppressive therapy.

   **Level of Evidence:** C.

**Class IIb:**

1. Desensitization therapy should be considered when the calculated PRA is considered by the individual transplant center to be high enough to significantly decrease the likelihood for a compatible donor match or to decrease the likelihood of donor heart rejection where unavoidable mismatches occur.

   **Level of Evidence:** C.

2. Choices to consider as desensitization therapies include IV immunoglobulin (Ig) infusion, plasmapheresis, either alone or combined, rituximab and, in very selected cases, splenectomy.

   **Level of Evidence:** C.
3. A large randomized controlled clinical trial is needed to assess the effectiveness of desensitization strategies and their impact on outcomes after HT.

Level of Evidence: C.

Methods for Monitoring Allosensitization Status of Patients before and After Heart Transplantation

Currently, there are no universally accepted standards for the pre-operative monitoring of anti-HLA antibodies, circulating immunoglobulins or lymphocyte subpopulations in allosensitized patients. The presence of anti-HLA antibodies is regularly monitored in allosensitized patients undergoing desensitizing therapies until a compatible heart allograft becomes available.250 In ambulatory, non-sensitized HT candidates, it is reasonable to screen for anti-HLA antibodies every 6 months. In HT candidates requiring blood transfusions, anti-HLA antibody level determination should be repeated 2 to 4 weeks later and prospective donor recipient crossmatch is required if a suitable donor organ becomes available in the interim period. No uniform recommendations exist as to the frequency of antibody monitoring after an infection or during MCS (Table 3).

As stated in the section pertaining to desensitization therapies, circulating immunoglobulins are measured before and after immunoabsorption and plasmapheresis, and lymphocyte subpopulations before and after the use of rituximab.

In addition to the post-operative retrospective crossmatch, donor-specific antibodies levels should be obtained when AMR is suspected or confirmed by EMB.

Although some reports suggest a correlation between increased levels of soluble HLA class I molecules (sHLA-I) and HT rejection, their determination is not routinely done in the clinical setting.261

Measurement of donor-specific antibodies level should be done if the finding of positive C4D staining in EMB tissue suggests the presence of AMR.261 In addition, monitoring donor-specific class I and class II HLA antibodies after transplantation has been used as a diagnostic/prognostic tool for AMR.254, 258

Recommendations for Monitoring of Allosensitization Status of Heart Transplant Candidates and Recipients250, 252, 260:

(Table 6)

Class IIb:

1. The presence of anti-HLA antibodies should be regularly monitored in allosensitized patients undergoing desensitizing therapies until a compatible heart allograft becomes available.

Level of Evidence: C.

2. In ambulatory, non-sensitized HT candidates it is reasonable to measure anti-HLA antibodies every 6 months.

Level of Evidence: C.

3. In HT candidates requiring blood transfusions, anti-HLA antibodies determination should be repeated 2 to 4 weeks later and prospective donor/recipient crossmatch is required in the interim period if a suitable donor organ becomes available.

Level of Evidence: C.

4. No uniform recommendations exist as to the frequency of anti-HLA antibody determinations after an infection or during MCS.

Level of Evidence: C.

5. Circulating immunoglobulins should be measured before and after plasmapheresis or immunoabsorption.

Level of Evidence: C.

6. Lymphocyte subpopulations should be measured before and after the use of rituximab.

Level of Evidence: C.

7. In addition to the post-operative retrospective crossmatch, donor-specific antibodies levels should be obtained when AMR is suspected or confirmed by EMB.

Level of Evidence: C.

Hyperacute Rejection and Delayed Antibody-Mediated Rejection

Hyperacute rejection occurs in the presence of a positive crossmatch and high levels of donor-specific antibodies that are preformed and circulating in the recipient that leads to immediate and overwhelming heart allograft failure shortly after reperfusion. It is characterized by a cytotoxic complement mediated antibody reaction and most often occurs in the setting of preformed antibodies directed against epitopes of the HLA system or ABO system. Allosensitized patients who are sensitized may avoid hyperacute rejection by desensitization strategies (described above) and, most commonly, by acceptance only of donors with “acceptable antigens” and/or low level or “weak” antibody responses. Despite manoeuvres to avoid hyperacute rejection sensitized recipients have a lower survival than those with PRA < 10% and appear to experience delayed AMR associated with elevated titers of donor specific antibodies.252
Table 6  Panel-Reactive Antibody Screening Frequency After Original Assessment

<table>
<thead>
<tr>
<th>PRA</th>
<th>1 mon</th>
<th>2 mon</th>
<th>3 mon</th>
<th>4-6 mon</th>
<th>1 year</th>
<th>Variable</th>
<th>SE</th>
<th>Other</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>10</td>
<td>2</td>
<td>8</td>
<td>16</td>
<td>7</td>
<td>4</td>
<td>16</td>
<td>2</td>
<td>65</td>
</tr>
<tr>
<td>Positive</td>
<td>33</td>
<td>8</td>
<td>6</td>
<td>2</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>65</td>
</tr>
</tbody>
</table>

PRA, panel-reactive antibody; SE, sensitizing events.
Adapted from Betkowski AS, et al. 250

Acute AMR is observed in allosensitized patients and is associated with inferior HT survival. The incidence may be up to 15% in the first year after HT and the clinical presentation has no pathognomonic features. Histological features include myocardial capillary injury with endothelial-cell swelling and intravascular macrophage accumulation. If these pathologic abnormalities occur in the presence of unexplained HT dysfunction, with or without symptoms of hemodynamic compromise, immunostaining can be performed to look for capillary deposition of immunoglobulin (IgG, IgM and/or IgA) plus complement (C3d, C4d and/or C1q) by immunofluorescence on frozen sections, CD68 staining of macrophages within capillaries (CD31- or CD34-positive) by immunohistochemistry, and C4d staining of capillaries by paraffin immunohistochemistry. 262

Level of Evidence: C.

2. Rituximab can be added to reduce the risk of recurrent rejection.

Level of Evidence: C.

3. Changes in therapy that can be considered for maintenance immunosuppression in patients who experience AMR can include switch to tacrolimus (TAC) in patients receiving cyclosporine (CYA)-based immunosuppression, increased doses of mycophenolate mofetil (MMF) and CS.

Level of Evidence: C.

Allosensitization in Pediatric Heart Transplant Recipients

The frequency of HLA sensitization is increasing in the pediatric population due to the greater number of patients with complex congenital heart disease undergoing palliative surgical procedures with exposure to blood products and valved or non-valved allograft materials. These can induce a strong HLA class I and class II antibody response that can persist for up to 8 years after allograft implantation. 242, 264, 265 In addition, the increasing application of pediatric MCS technology for end-stage heart failure has led to an unprecedented occurrence of allosensitization in children with cardiomyopathy. 243

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The requirement of a negative prospective crossmatch in critically ill children can negatively impact survival because it inevitably prolongs the waiting time for a donor organ. A retrospective analysis of HT candidates since 1990 (n=252), for which CDC allo-antibodies data were available, demonstrated that allosensitization influences both pre- and post-HT outcomes. 24 Of 252 subjects, 38 (15%) had pre-operative allosensitization, defined as a PRA > 10%. At 1 year after listing, sensitized subjects had a higher mortality than non-sensitized subjects (22% vs. 8.4% p=0.055). Survival at all time points after listing (regardless of transplantation) was worse for sensitized subjects (p = 0.04).

Although no statistically significant differences in post-operative graft or patient survival were noted, allosensitization
before HT was associated with decreased freedom from CAV (hazard ratio 2.76, 95% confidence interval 1.18 to 6.45; \( p = 0.019 \)). Because of the high wait-list mortality for sensitized pediatric HT recipients, protocols for peri-operative antibody removal without a prospective crossmatch have been developed and utilized in some centers with reasonable success. In 31 pediatric procedures, HT recipients with a positive CDC crossmatch, the median B- and T-cell PRA were, respectively, 76% and 52%. Almost 50% of the recipients were older than 1 year of age at HT. Therapies in most cases were intra-operative plasma exchange/plasmapheresis, post-HT plasmapheresis, and drug therapy using TAC, MMF, CS, and IV Ig. Survival rates at 1 year were 84%, and probability of survival at 3 and 5 years were, respectively, 79%, and 70%, similar to the overall US transplant survival rates (www.unos.org). More than 70% of the subjects experienced acute rejection events. However, the frequency of rejection with hemodynamic compromise varied widely (0-60%) between centers. Most acute rejection episodes developed early, and C4d or C3d positivity generally disappeared after the first few months. Evaluation of incidence of CAV is ongoing, but survivors have normal graft function. Age did not influence outcomes. \(^{245, 266}\)

Data on the impact of desensitization strategies are even more limited in the pediatric than in the adult population. Results of desensitization procedures in children remain inconclusive, because antigenic stimuli, such as devices and allograft materials remain in place during therapy. Given the inability to predict the timing of donor organ availability, the potential morbidities associated with the available desensitization therapies and the acceptable intermediate outcomes of HT despite a positive crossmatch, most centers do not practice desensitization strategies in highly sensitized pediatric patients.

**Recommendations for the Approach to Allosensitization in Pediatric Heart Transplant Recipients** \(^{244, 245, 266}\)

**Class IIb:**

1. The HT can be carried out in highly sensitized pediatric patients without a prospective crossmatch or virtual crossmatch at centers experienced in pediatric HT across a positive crossmatch.

**Level of Evidence:** C.

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**Topic 4: Management of ABO “Incompatible” Pediatric Heart Transplants**

**Overview**

When compared to older recipients, infants with severe congenital cardiac malformations or cardiomyopathies awaiting HT are known to be at greater risk of dying due to the paucity of appropriately sized organ donors. This small pool has provided compelling motivation to challenge previous mandates against the usage of certain donors, such as those of incompatible blood groups. \(^{267}\)

Among potential HT candidates, infants are particularly suited for this approach because of an immature immune system that precludes T-cell independent responses. \(^{268}\) Taking advantage of this natural lag in immune responsiveness, the Toronto group reported a protocol in which infants intentionally received ABO-incompatible heart allografts. None of the infants received aggressive pre-operative immunosuppression for antibody removal, and those who had positive antibody titers underwent plasma exchange using the CPB circuit at the time of HT. Short-term outcomes were excellent, without a single patient developing hyperacute rejection. \(^{269}\) Since the original report, centers have increasingly adopted the practice of ABO-incompatible HT with short-term results similar to those of the original Toronto cohort. \(^{270, 275}\) At the present time, intermediate-term results appear equivalent to those reported for ABO compatible pediatric HT recipients. \(^{271, 276}\)

The safety and feasibility of pediatric ABO-incompatible HT with the use of intra-operative plasma exchange has been established. \(^{269}\) This strategy improved the likelihood of HT and reduced infant waiting list mortality. \(^{271, 275, 277}\) These data led to a UNOS policy change in September 2006 allowing the listing for HT of infants across the ABO blood group barrier. \(^{278}\)

For neonates and infants undergoing ABO-incompatible HT, in addition to the routine peri-operative management, further attention must be paid to issues related to blood product transfusion. Every effort must be made to avoid blood products that may contain donor-specific antibodies, as this may lead to AMR.

**Patient Selection**

Suitability for ABO-incompatible HT is ultimately based on the stage of immunologic maturation of the candidate at the time of evaluation. While age may correlate with the time of development of isohemagglutins, it is the titers of these antibodies that become critical in patient selection. There are several reports in the literature of successful ABO-
incompatible HT beyond the infancy period in patients who were 2, 3.5, and 5 years of age and who lacked isohemagglutinins. However, age itself is clearly not the primary risk indicator, and serves only as a surrogate marker for an individual’s ability to produce isohemagglutinins. Even for infants who have begun to produce isohemagglutinins, the absolute titer above which HT is contraindicated remains unclear. Successful HT even in children with donor-specific isohemagglutinin titers as high as 1:64 has been reported. Five patients in the Toronto cohort with pre-operative isohemagglutinin titers ranging from 1:8 to 1:128 underwent successful HT without AMR and minimal re-accumulation of anti-donor antibodies after HT. Therefore, the absolute upper limit of age or isohemagglutinin titers remain unclear.

Recommendations for the Selection of Candidates for ABO “Incompatible” Heart Transplant:

Class IIa:
1. The upper limit of age or isohemagglutinin titer for ABO-incompatible pediatric HT remains unclear.
   
   Level of Evidence: C.

2. ABO-incompatible HT can be safely performed in the pediatric population in the presence of positive isohemagglutinin titers against the donor organ.
   
   Level of Evidence: C.

3. ABO-incompatible HT, especially in the presence of donor specific isohemagglutinins > 1:4, should be performed in an experienced center.
   
   Level of Evidence: C.

Intra-operative Management

Intra-operative management of ABO-incompatible infant HT recipients remains the same as initially described in the original Toronto cohort. Briefly, all patients should have isohemagglutinin testing before surgery. The CPB circuit is primed with plasma as appropriate for the particular donor-recipient blood group combination (Table 7). Approximately 2 to 3 times the total body plasma volume is exchanged during the initiation of CPB to remove donor-specific isohemagglutinin, which are remeasured before the release of the aortic cross-clamp to ensure a negative or low donor-specific titer (<1:4). With the utilization of pre-operative plasma exchange, there have been no reported cases of hyperacute rejection.

Recommendation for the Intra-operative Care of ABO “Incompatible” Heart Transplant Recipients:

Class IIa:
1. ABO-incompatible HT can be undertaken by performing plasma exchange using the CPB circuit to remove donor-specific isohemagglutinins.
   
   Level of Evidence: C.

2. Plasma exchange using the CPB circuit allows the safe transplantation of ABO-incompatible organs without the need of aggressive pre-operative immunosuppressive therapies or splenectomy.
   
   Level of Evidence: C.

Isohemagglutinins and Their Follow-up

Titers of isohemagglutinins are measured with standard agglutination tests. Isohemagglutinins should be measured at progressively longer intervals in the early post-operative period. ABO-incompatible heart transplant recipients who develop rising titers of isohemagglutinins post-operatively should be assessed for evidence of graft dysfunction (e.g., hemodynamics, echocardiography, biopsy as per institutional protocol, and/or clinical suspicion). In the short-term, most patients do not develop rising titers of isohemagglutinins. In the few that do, concern and/or evidence for AMR have been very rare. In the 2 patients with reported AMR in the Toronto cohort, management similar to that of the sensitized population with a course of plasmapheresis and augmentation of immunosuppression was successful.

Recommendations for the Monitoring of Isohemagglutinin Levels in ABO “Incompatible” Heart Transplant Recipients:

Class IIa:
1. Serial measurements of isohemagglutinin titers should be done in the post-operative period. Decisions as to whether immunosuppressive therapy must be modified should be based not only on the change in isohemagglutinin titers but also on clinical or pathological evidence of rejection.
   
   Level of Evidence: C.
Table 7: Match of Blood Products to Specific ABO-Incompatible Heart Transplant Scenario

<table>
<thead>
<tr>
<th>Blood group</th>
<th>Red blood cells (plasma depleted)</th>
<th>Fresh frozen plasma</th>
<th>Cryoprecipitate</th>
<th>Platelets (managed similarly to plasma)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>A</td>
<td>O</td>
<td>A</td>
<td>A or B concentrate</td>
</tr>
<tr>
<td>O</td>
<td>B</td>
<td>O</td>
<td>B</td>
<td>B concentrate</td>
</tr>
<tr>
<td>O</td>
<td>AB</td>
<td>O</td>
<td>AB</td>
<td>AB, A or B concentrate</td>
</tr>
<tr>
<td>A</td>
<td>B</td>
<td>A</td>
<td>AB</td>
<td>AB, or B² concentrate</td>
</tr>
<tr>
<td>A</td>
<td>AB</td>
<td>A</td>
<td>AB</td>
<td>AB, or A² concentrate</td>
</tr>
<tr>
<td>B</td>
<td>A</td>
<td>B</td>
<td>AB</td>
<td>AB, or A² concentrate</td>
</tr>
<tr>
<td>B</td>
<td>AB</td>
<td>B</td>
<td>AB</td>
<td>AB, or B² concentrate</td>
</tr>
</tbody>
</table>

*Second choice.

**Blood Product Management Following ABO-Incompatible Transplantation**

For children receiving blood products at any time post-operatively it is mandatory to avoid blood products containing antibodies that would be detrimental to both donor and recipient. Therefore, it is imperative to carefully select plasma products and platelets of the appropriate blood group, as these preparations contain large quantities of immunoglobulins.²⁸⁰ Table 7 provides the reader with the appropriate matching of blood products to specific recipient and donor combinations. Whole blood transfusions must be avoided in a recipient of an ABO-incompatible HT, and the families of these children should be instructed to inform future medical care providers that in case of surgeries and emergencies any blood product must appropriately match to the child’s situation. Parents can easily understand and remember the information that group O red blood cells and group AB blood elements are safe for every blood group combination. The children’s families can be provided with written instructions that can be shared with the health care provider to minimize the likelihood of errors.

Platelet preparations require special attention because the handling of these blood elements is more similar to that of plasma products rather than to that of red blood cells (Table 7). The reason for this practice is because platelet preparations contain very low levels of ABH antigens and large amounts of plasma.²⁸⁰

**Recommendations for the Administration of Blood Products in ABO “Incompatible” Heart Transplant Recipients**²⁶⁹,²⁷¹,²⁷⁷

(See Table 7)

**Class IIa:**

1. Whole blood products should never be administered to a child who has received an ABO-incompatible HT, and the families should be educated to communicate this fact to other care givers in the case of any future medical emergency or surgery. Group O red blood cells and group AB blood elements are safe for every blood group combination.

   **Level of Evidence: C.**

2. If red blood cell transfusions are given to any ABO-incompatible HT recipient, red blood cell units should be matched based on the HT recipient’s ABO blood type.

   **Level of Evidence: C.**

3. If platelets and/or plasma preparations are needed in ABO-incompatible HT recipients, these blood products should be matched based on the donor’s ABO blood type.

   **Level of Evidence: C.**

**Immunotherapy**

For patients undergoing ABO-incompatible HT, standard (triple) maintenance immunosuppressive therapy has been used routinely as per institutional protocol including (a) a CNI (TAC or CYA), (b) an antiproliferative agent (MMF or AZA), and (c) CSs.²⁶⁹-²⁷⁵,²⁸¹,²⁸² All except 1 report have included the use of anti-thymocyte globulin (ATG) as an induction agent in the peri-operative period.²⁷⁵ The CSs are administered prior to cross-clamp removal, and are weaned quickly over the course of days to weeks. The results of all intermediate-term reports confirm that immunosuppression in infant recipients of an ABO-incompatible HT should not differ from that of all other pediatric HT recipients, including CS-free maintenance immunosuppression.²⁶⁹-²⁷⁶
Recommendations for Immunosuppression in ABO “Incompatible” Heart Transplant Recipients

**Class IIa:**
1. Standard (triple) immunosuppression with a CNI, an antiproliferative agent, and CSs can be used in children undergoing ABO-incompatible HT without an increased risk of rejection.
   
   **Level of Evidence: B.**
2. Immunosuppression management beyond the peri-operative period is similar to that of the ABO-compatible pediatric HT population.
   
   **Level of Evidence: B.**

Rejection Surveillance

Episodes of cellular rejection in the ABO-incompatible HT population do occur, but mirror those seen in the ABO-compatible HT recipients. Surveillance in the pediatric ABO-incompatible HT patient is carried out according to standard protocol, and it is modified only when clinical signs of rejection occur. Rejection episodes requiring intensification of immunosuppression should be treated according to the guidelines described in Task Force 2.

**Recommendation for Rejection Surveillance in ABO “Incompatible” Heart Transplant Recipients:**

**Class IIa:**
1. Rejection surveillance in ABO-incompatible HT recipients is the same as that of the ABO-compatible HT population.
   
   **Level of Evidence: C.**

**Topic 5: Coagulopathies with Heart Transplant Surgery**

Introduction

**Coagulopathy in Cardiac Surgery**

Coagulopathies are common after all types of cardiac surgery. It is estimated that blood transfusions are needed in 80% of all cardiac surgery patients. Nearly 15% of all blood products in the US are used in association with cardiac surgery. Of all patients undergoing cardiac surgery, 20% are prone to peri-operative hemostatic abnormalities that require surgical revision in 2% to 6% of all patients. Cardiac surgery-related factors that contribute to coagulopathies include platelet consumption and dysfunction, hemodilution with consumption of clotting factors, hypothermia, activation of the inflammatory cascade, and fibrinolysis. Different studies consistently find advanced age, increased pre-operative sCr level, small body surface area, emergency surgery, low temperature during CPB, duration of extracorporeal circulation (> 150 minutes), combined valvular revascularization surgery, number of bypass grafts (≥ 5), reoperative surgery, and pre-operative antiplatelet therapy to be risk factors for bleeding in cardiac surgery.

**Coagulopathy in Heart Transplantation**

HT recipients have additional risk factors for peri-operative bleeding including recipient’s coagulopathy, need for repeat median sternotomy, and a prolonged CPB. Various factors contribute to a recipient’s coagulopathy. First, many patients are on anticoagulation pre-operatively for poor LV function, AF, mechanical valves, or MCS. In the pediatric population, patients with complex congenital heart disease after multiple corrective procedures with or without allograft material, patients being transplanted from ECMO, and chronically cyanotic patients with extensive collaterals are often very challenging in terms of peri-operative hemostasis. Hepatic or renal dysfunction associated with heart failure can also contribute to coagulopathies. Amiodarone-treated HT recipients have greater peri-operative bleeding. Many HT recipients have greater bleeding because native heart explantation is complicated by adhesions due to prior surgeries.

As therapies for advanced heart failure evolve, a greater number of patients receive MCS as a bridge to HT. With the exception of the Jarvik VAD which is placed through a thoracotomy, most VADs are implanted through a sternotomy and the resulting scarring remains a major source of HT surgical bleeding. In addition, except for patients with the HeartMate XVE, recipients of MCS require warfarin anticoagulation, which is intensified if VAD-related clotting problems occur. However, in some retrospective studies, the use of warfarin has not been shown to increase the risk of operative bleeding.

**Coagulation**

Bleeding in cardiac surgery can be broadly divided into 2 categories: surgical bleeding (at an anastomotic site, from a vessel, or at a suture line) or non-surgical bleeding (coagulopathy). This review is mainly focused on non-surgical bleeding. Hemostasis has been described in detail elsewhere. Briefly, the coagulation cascade consists of an extrinsic system activated by a tissue factor (thromboplastin), an intrinsic system activated by contact with surfaces, and a common pathway. The complexity of the coagulation cascade is further enhanced by the discoveries of
tissue factor expressing cells and platelets in a hemostatic process that include initiation, amplification and propagation. From the initial steps of homeostasis, both platelets and coagulation activation are amplified. Thrombin is a key activator of clotting through pathways that include platelet activation and the formation of a fibrin clot as well as the clot dissolving aspect with thrombomodulin and the release of tissue plasminogen activator (t-PA). The final product of this cascade is thrombus at the site of vascular injury, limitation of clot propagation, and a time delayed process of vessel recanalization.

Coagulopathy With Cardiopulmonary Bypass

In cardiac surgery, the use of the extracorporeal surface of the CPB circuit disrupts the normal homeostatic mechanisms that maintain blood fluidity. During extracorporeal circulation, a decrease of coagulation factors and platelets as well as an activation of fibrinolysis is observed. First, the hemodilution caused by priming of the extracorporeal circuit can contribute to this decrease. Further, there is activation and denaturation of these coagulant proteins by the artificial surfaces. Thrombin, which is continuously generated during CPB, can be measured intra-operatively despite administration of high heparin doses being administered. Platelets are activated by the thrombin, fibrinogen bound to the circuit, and the shear forces of contacting the surface. In addition, the circuit has no endothelial cells that normally continuously suppress platelets activation. With activation during CPB, platelets become refractory to subsequent stimuli and are dysfunctional after CPB. Approaches to reduce platelet activation include controlled use of suction, avoidance of air bubbles, and use of heparin-coated bypass materials or more biocompatible extracorporeal circuits. Further, pro-inflammatory proteins such as kallikrein and complement also become activated by the extracorporeal circuit, which leads to the activation of leucocytes, endothelial cells and the systemic release of cytokines. This cascade results in inflammation that promotes abnormal hemostasis and increases the risk of multi-organ failure.

Fibrinolysis, also activated by CPB, ceases with discontinuation of the circuit. Perhaps increased fibrinolysis is induced by the coagulation factors via activation of factor XII and thrombin which in turn stimulate the release of tissue plasminogen activator from the endothelium.

Hypothermia can also alter the clotting mechanisms. Changes in platelet aggregation in patients undergoing hypothermic CPB at 27°C to 28°C have been seen. Conventional tests of the hemostatic mechanisms are done at 37°C, which limits the detection of some of the clotting defects during hypothermia.

Thus, IV heparin is used to prevent the catastrophic clotting that can occur in an extracorporeal circuit. Heparin is a heterogeneous glycosaminoglycan closely related to the endogenous heparan present on the surface of endothelial cells and in the extracellular matrix. This compound binds to antithrombin with high affinity. This complex results in a thousand-fold increase in binding affinity to thrombin and factor Xa. High-dose heparin (300 to 400 U/kg) is routinely used to anticoagulate patients before initiation of CPB. Heparin dosing has been empirically established from the activated clotting time (ACT) as the dose at which clotting no longer occurs in the circuitry. Thus, many surgical teams strive to keep an ACT > 400 seconds even though lower levels may be effective. The main advantage of heparin is that its anticoagulant effects can be reversed with the use of protamine, which combines with heparin into a complex devoid of anticoagulant effects. The efficacy is dependent on the heparin-protamine ratio of 1:1 to 1:3. High doses of protamine can cause inhibition of coagulation and platelet aggregation and can paradoxically increase the risk of bleeding. In addition, rapid injection of protamine can cause histamine release and hypotension. It can also produce life-threatening pulmonary hypertension. Thus, minimization of protamine dosage is preferred. The ACT is used to gauge reversal of heparin effects. The goal is usually to achieve a level < 130 seconds or within 10% of the pre-CPB value.

Testing to Evaluate Hemostasis in Cardiac Surgery

Pre-operative evaluation of hemostasis must include knowledge of the patient’s renal and hepatic function and treatment with platelet inhibitors and oral anticoagulants. Pre-operative evaluation should include determination of the activated partial thromboplastin time (aPTT) and prothrombin time (PT). This evaluation, however, falls short of accurately predicting the risk of bleeding with cardiac surgery and of detecting defects of primary hemostasis, such as von Willebrand disease and platelet dysfunction.

At a minimum, intra-operative assessment of hemostasis should include measurement of ACT due to its ability to monitor high heparin concentrations used during CPB. Limitations of ACT testing include variability of commercially available devices and alterations in values with the administration of aprotinin. The use of thromboelastography, which measures the physical strength of the fibrin clot during the coagulation process, has been shown to improve diagnosis of intra-operative bleeding and to reduce the need for blood transfusions. However, pre-operative...
thromboelastography has limited ability to predict blood loss during cardiac surgery.

Platelet function is the other important determinant of operative bleeding. Platelet counts > 100,000/uL are generally considered adequate for surgical hemostasis. Although platelet aggregometry is the “gold-standard” test of platelet function, easier point of care assays, such as the one using the platelet function analyzer-100 (PFA-100) are typically employed during cardiac surgery. In these assays, whole blood is used to test the time required for platelets to plug a hole in a collagen-coated cartridge through which blood is forced to flow. The ability of these assays to predict the risk of intra-operative bleeding is uncertain.319, 321, 322

Tests of fibrinolysis include fibrinogen levels and D-dimer values. Fibrinogen is converted to fibrin by thrombin in route to becoming a clot. Levels can be directly measured, with normal values being in the range of 150 to 400 mg/dL. A fibrinogen level > 100 mg/dL is adequate for hemostasis. Fibrinolysis is a process in which plasmin cleaves cross-linked fibrin to produce dimeric units (D-dimer). Values of D-dimer values correlate with the level of fibrinolysis present in the surgical patient and with the risk of bleeding after cardiac surgery.323

Most tests of hemostasis have not been evaluated in randomized clinical trials. Assay values considered significant are derived from clinical bleeding but not specifically from that occurring during cardiac surgery.

**Recommendations for the Evaluation of Hemostasis in Heart Transplant Recipients314:**

**Class I:**

1. A history of bleeding (including details of family history, previous excessive post-traumatic or post-surgical bleeding) and of the use of any medications that alter coagulation should be obtained from the patient.

   **Level of Evidence: C.**

2. Screening coagulation tests of PT, aPTT, and platelets count should be measured immediately before HT surgery.

   **Level of Evidence: C.**

3. The ACT should be obtained at multiple points during the HT surgery to gauge the activity of heparin during each phase of the HT surgery.

   **Level of Evidence: C.**

**Class IIa:**

1. Thromboelastography may be useful during the HT surgery to further elucidate the status of the patient’s hemostasis.

   **Level of Evidence: C.**

2. Platelet function can be measured either by platelet aggregometry or by a point of care assay such as the platelets function assay 100 (PFA-100) during the HT surgery.

   **Level of Evidence: C.**

3. Fibrinogen levels and D-Dimer values should be measured post-operatively because these are tests of fibrinolysis and correlate with the risk of bleeding after HT surgery.

   **Level of Evidence: C.**

4. Thromboelastography may be repeated after HT surgery to monitor patients’ hemostasis.

   **Level of Evidence: C.**

**Reversal of Anticoagulation before Heart Transplantation**

In patients chronically anticoagulated with warfarin undergoing cardiac surgery, including HT, the risk of bleeding is likely to be increased when the international normalized ratio (INR) is ≥ 1.5. Therefore, it is reasonable to reduce the INR to this level at the time of surgery.324 Several therapies are available for the reversal of oral anticoagulation, and these include oral or IV vitamin K, human fresh frozen plasma (FFP), prothrombin complex concentrates (PCCs), and recombinant active factor VII (rFVIIa).325 Vitamin K alone is inappropriate if rapid normalization of the INR is required, because the onset of action is 4 to 6 hours after IV administration and at least 24 hours after oral administration.324 Therefore, when rapid reversal of warfarin is needed, vitamin K at doses of 2.5 to 5 mg should be administered IV in conjunction with FFP, PCCs, or rFVIIa.325

The PCCs are concentrates of essential coagulation factors, often including factors II, VII, IX, and X.326 Whereas in the US, PCCs and rFVII are not approved by the FDA for reversal of anticoagulation, in Europe these substances are approved specifically for this indication. The PCCs are appropriate for emergency reversal of oral anticoagulation because of their rapid onset of action. A dose of 500 U (typically approximately 7 U/kg) is effective for rapid correction of an INR < 5, but higher doses (up to 50 U/Kg) may be necessary in patients with INR values above this level.327
Comparative studies have demonstrated that PCCs are more effective than FFP for correcting patients’ INRs. In one such study, the mean post-treatment and lowest INR values in patients receiving 4 units of FFP were, respectively 2.3 and 1.6, compared with 1.3 in patients receiving PCC at a dose of 25 to 50 U/kg.\textsuperscript{328-332} Also, post-treatment levels of factor IX were much lower in the FFP group than in the PCC group (19 vs. 68.5 U/dL). Similarly, in a second study, only 1 of 6 patients receiving 4 units of FFP achieved a safe INR level < 1.5, compared with 5 of 6 patients receiving PCC (50 U/kg).\textsuperscript{325} In this study, the mean correction time was 41 minutes with PCC, significantly shorter than the 115 minutes observed with FFP. The time required for INR correction was reported to be 4 to 5 times shorter with PCC. Another advantage of PCCs over human plasma is that smaller volumes of PCCs are required to reverse anticoagulation, because the concentration of clotting factors in PCCs is approximately 25 times higher than that in human plasma.\textsuperscript{326, 332} Although human plasma is often administered at doses approximately 15 mL/kg, double human plasma doses or 2.4 L in an 80-kg patient, are required to reverse anticoagulation in critically ill patients.\textsuperscript{325} In contrast to FFP, recommended doses of PCC can be delivered at a volume of 1 to 2 mL/kg. With PCCs the smaller volumes minimize the risk of worsening fluid overload and shorten infusion time.\textsuperscript{325} Compared to FFP, PCCs can be prepared faster, can be stored at room temperature, avoiding the need for thawing and warming, and do not require crossmatching before administration. Thus the time from patient presentation to correction of INR is much shorter with PCCs than with FFP (15 min vs. 1-2 hr).\textsuperscript{326} The PCCs may also be associated with lower risks of viral or prion contamination and of transfusion-related acute lung injury (TRALI), a major cause of death after transfusion.\textsuperscript{325} The PCCs have been associated with a modest risk of thrombogenic events.

Although preliminary studies have demonstrated the safety and efficacy of rFVIIa for anticoagulation reversal, this modality is not yet approved in either the US or Europe. Advantages of rFVIIa over FFP are similar to those of PCCs, including low infusion volume and rapid administration time, but comparative studies are lacking.\textsuperscript{325, 333}

\textbf{Recommendations for the Reversal of Anticoagulation before Heart Transplantation}\textsuperscript{324, 326, 328, 332}:

\textit{Class I:}

1. Pre-operatively, the INR should be reduced to \( \leq 1.5 \).

\textit{Level of Evidence: C.}

2. Low doses of vitamin K (2.5-5.0 mg) given IV are preferable to high doses because they are associated with a lower risk of anaphylaxis.

\textit{Level of Evidence: C.}

3. Given the need for rapid normalization of the INR, chronically anticoagulated patients about to undergo HT should receive vitamin K in conjunction with FFP, PCCs, or rFVII depending on their availability and the patient’s renal and hepatic functions.

\textit{Level of Evidence: C.}

\textbf{Peri-operative Management of Heart Transplant Recipients with Heparin-Induced Thrombocytopenia}

Heparin-induced thrombocytopenia (HIT) is an immune-mediated disorder characterized by the formation of antibodies against the heparin-platelet factor 4 complex. The frequency of HIT ranges from 0.2\% to 5.0\% in patients exposed to heparin for more than 4 days. In addition to duration of therapy, the 3 factors most strongly associated with the development of HIT include use of unfractiected rather than low-molecular-weight heparin, surgical rather than medical setting, and female gender.\textsuperscript{334}

There are a number of anticoagulants that can be used instead of heparin in patients with HIT including a direct thrombin inhibitor such as lepirudin (recombinant hirudin), bivalirudin, or argatroban; or danaparoid. To date, no prospective randomized studies have compared the relative efficacy and toxicity of the available agents. However, because of their different modes of excretion and inactivation, patients with HIT and renal insufficiency are usually treated with argatroban, whereas those with hepatic impairment are typically given lepirudin.

Lepirudin (Refludan\textsuperscript{\textregistered}) is a recombinant hirudin approved by the FDA for the treatment of HIT complicated by thrombosis. A starting dose of lepirudin \( \leq 0.10 \) mg/kg/hr has been recommended in patients with serum creatinine \( < 1 \) mg/dL. Because the drug undergoes renal clearance and anticoagulant effect is not easily reversed, doses must be decreased in patients with renal insufficiency and the aPTT must be closely monitored to avoid drug accumulation.\textsuperscript{335}

Bivalirudin (Angiomax), a hemodialyzable direct thrombin inhibitor and hirudin analog has been successfully employed in patients with HIT, with reduced doses safely employed in patients with combined hepatic and renal failure. It is approved by the FDA for patients with, or at risk of, HIT who are undergoing percutaneous coronary intervention. The recommended initial dose of bivalirudin for HIT is approximately 0.15 mg/kg/hour, adjusted to achieve an aPTT
of 1.5 to 2.5 times the baseline value. Doses of 0.14 mg/kg/hour in patients with hepatic dysfunction and 0.03 to 0.05 mg/kg/hour in patients with renal or combined hepatic and renal dysfunction have been successfully employed. The development of anti-hirudin antibody formation can occur with longer treatment.

Argatroban is a direct thrombin inhibitor with a short in vivo plasma half-life of 24 minutes; and its effect is monitored by the aPTT. In patients with normal hepatic function, the standard starting dose is 2 µg/kg/min by continuous IV infusion, adjusted to maintain the aPTT at 1.5 to 3 times the baseline value. Due to hepatobiliary elimination, a lower starting dose (0.5-1.2 µg/kg/min) is appropriate in patients with hepatic dysfunction, combined hepatic/renal dysfunction, heart failure, or anasarca.335 In such patients, the aPTT should be checked at 4-hour intervals after drug initiation or dose change to ensure that the desired level of anticoagulation is present. An even lower starting dose of argatroban (0.2 µg/kg/min) may be appropriate in critically ill patients with multiple organ dysfunction and HIT.335

Danaparoid (Orgaran®) is a heparinoid that includes predominantly dermatan sulfate and low-sulfated heparan sulfate. It is available in many countries but not in the US. It has been given to patients with HIT or a history of HIT who require CPB. The recommended dose includes an initial IV bolus of 2250 U, modified up or down according to body weight, followed by an IV infusion of 400 U/hr for 4 hours, 300 U/hr for the next 4 hours, and 200 U/hr thereafter. Doses are adjusted to achieve anti-Xa levels of 0.5 to 0.8 U/mL. Disadvantages of danaparoid include the need to measure anti-factor Xa levels, its long half-life (25 ± 100 h), renal elimination, and the absence of an antidote.335

Other approaches, including plasmapheresis, are not effective for the treatment of HIT and should not be used in place of the compounds described above.

Patients with a history of HIT who require CPB have been successfully anticoagulated with a brief course of unfractionated heparin without complications. This approach is based on the theory that a secondary immune response after re-exposure to heparin is unlikely to occur until at least 3 days later. Thus, a brief exposure to heparin during CPB should not immediately elicit HIT antibodies. Furthermore, because heparin is rapidly cleared after the procedure, even if antibodies appeared, they would not be thrombogenic in the absence of heparin. In a report of 3 patients with HIT requiring urgent HT, re-exposure to unfractionated heparin in the absence of heparin-induced platelet aggregation (HIPA) was uneventful.336 Heparin was discontinued and a direct thrombin inhibitor (agatrotan or lepirudin) was used for a few hours post-operatively in all 3 cases to prevent recurrence of thrombosis due to the re-exposure to heparin. Another report yielded similar results.337

**Recommendations for Anticoagulation in Heart Transplant Recipients**

**Class IIa:**
1. The absence of platelet factor 4/heparin antibodies should be confirmed.
   - **Level of Evidence:** C.
2. The use of unfractionated heparin should be restricted to the operative procedure itself. Low molecular weight heparin is not recommended, due to a longer half-life than unfractionated heparin and the inability to fully reverse its effect with protamine.
   - **Level of Evidence:** C.
3. Alternative anticoagulants can be used pre- and post-operatively in patients with history of HIT in whom the platelet count has recovered but IgG antibodies to the platelet factor 4/heparin complex are still present.
   - **Level of Evidence:** C.
4. Patients with abnormal hepatic and normal renal function can be treated with lepirudin, danaparoid, or fondaparinux, while those with abnormal renal and normal hepatic function can receive argatroban at standard doses or lepirudin at reduced doses.
   - **Level of Evidence:** C.
5. Patients with both renal and hepatic dysfunction can be treated with argatroban or bivalirudin at reduced doses.
   - **Level of Evidence:** C.

**Pharmacologic Management of Bleeding**

**Aprotinin**

Aprotinin is a potent inhibitor of the serine proteases including plasmin, thrombin, kallikrein, and activated protein C. The safety and efficacy of aprotinin in reducing bleeding during cardiac surgery has been demonstrated in several meta-analyses but has not been tested in large-scale randomized trials.338-341 In a cohort of HT recipients, aprotinin was found to significantly reduce bleeding in those with previous sternotomies but not in patients without prior surgeries.344 In addition,342, 343 a recent large observational study has shown an increased risk of renal failure, myocardial infarction or heart failure, and stroke or encephalopathy with the use of aprotinin in heart surgery patients.344 The results of this study triggered
a FDA warning regarding the risks of aprotinin. This drug should not be used in HT surgery.

**Tranexamic Acid and Epsilon-aminocaproic Acid**

Tranexamic acid and epsilon-aminocaproic acid are lysine analogues with antifibrinolytic activity. Both agents competitively inhibit the binding of plasmin to fibrinogen and t-PA to plasmin via lysine recognition sites required for fibrinolysis. Tranexamic acid is almost 10 times more potent than epsilon-aminocaproic acid. In contrast to aprotinin, neither agent is associated with an increased risk of end-organ damage. Epsilon-aminocaproic acid has been compared to aprotinin and found to have similar efficacy. Lysine analogues are indicated for the treatment of bleeding in a number of conditions but are not approved by the FDA for use in CPB despite evidence that their administration before CPB is associated with a 30% reduction in bleeding and blood transfusion requirement. Epsilon-aminocaproic acid is given as a loading dose of 75 to 150 mg/kg at the beginning of surgery followed by a continuous infusion at 10 to 15 mg/kg/hr. The dosage of tranexamic acid is 1/10 of epsilon-aminocaproic acid.

**Desmopressin**

Desmopressin, a vasopressin analogue with minimal vasopressor activity, stimulates the release of factors VIII:C and von Willebrand from the endothelium. Desmopressin only modestly reduces bleeding and its use is not routinely recommended.

**Transfusion Strategies for Bleeding**

Appropriate levels of coagulation factors are necessary for adequate surgical hemostasis. FFP administration should be guided by coagulation tests and measured deficiencies. No evidence exists for the prophylactic use of FFP to prevent bleeding. Goals of FFP administration should be to achieve 1.5 times the control mean of both the prothrombin time and the aPTT. Fibrinogen infusion is also important in massive bleeding. Levels drop with massive bleeding and subsequent red cell transfusions. Substitution should be done to maintain a level higher than 1 g/L.

Although platelet transfusions are common in cardiac surgery, few randomized trials support their routine use. Guidelines support the use of platelet transfusion when there is clinical evidence of microvascular bleeding in conjunction with excessive blood loss. A transfusion threshold of 50,000/uL is generally recommended. Prophylactic platelet transfusions during cardiac surgery are not useful in preventing bleeding and may be associated with an increase in pulmonary vascular resistance.

Recombinant FVIIa is not approved for bleeding during cardiac surgery, although case reports and small series have shown some efficacy in cases of excessive or refractory bleeding occurring during implant or explant of VADs and HT. Recombinant FVIIa combines with tissue factor at the site of injury and activates the coagulation cascade. However, because tissue factor is also expressed on monocytes and atherosclerotic blood vessels, it may have prothrombotic effects in cardiac surgery patients. Despite the potential efficacy of rFVIIa seems to have, prospective randomized trials with rFVIIa still do not confirm the efficacy or safety of this costly agent in cardiac surgery.

**Gaps in Evidence**

Transfusion strategies are not well studied. Consensus opinion drives the decision of when to transfuse blood products. Expert opinions on which clinical situations require transfusions are highly variable. Recombinant FVIIa has not been tested in controlled clinical trials and therefore there is little evidence to support its use in a bleeding cardiac surgery patient. Tranexamic acid and aminocaproic acid have not been evaluated in a definitive randomized study. Very few studies have been performed specifically in HT recipients. Thus, the recommendations for HT are extrapolated from evidence regarding achievement of hemostasis in general cardiac surgery.

**Recommendations for the Pharmacologic Management of Coagulopathies in Heart Transplant Recipients:**

**Class I:**

1. Transfusion of coagulation factors is necessary for adequate hemostasis. Thus, FFP and platelets should be transfused based on measured levels. Fibrinogen infusion for massive bleeding and inadequate fibrinogen levels is needed to control blood loss.

   **Level of Evidence: C.**

**Class IIa:**

1. Tranexamic acid and epsilon-aminocaproic acid both have anti-fibrinolytic activity and can be used prior to CPB to reduce the risk of bleeding in selected patients.

   **Level of Evidence: B.**

**Class IIb:**

1. Recombinant FVIIa may be used in cases of intractable or excessive bleeding with HT surgery.

   **Level of Evidence: C.**
Class III:
1. Although aprotinin can reduce bleeding during HT surgery, its routine use is not recommended due to an increased risk of adverse clinical events.
   **Level of Evidence: B.**
2. Desmopressin is not recommended for routine use because its modest reduction in bleeding has been associated with adverse clinical events.
   **Level of Evidence: A.**

Conclusion
Compared to patients undergoing general cardiac surgery, HT recipients have a greater incidence of coagulopathies due to multiple factors that include greater severity of illness in heart failure patients, more frequent use of anticoagulants, and protracted extracorporeal circulation in patients undergoing MCS explantation. There are several laboratory and point of care tests to assess the severity of the coagulopathy present in individual patients. The application of a combination of intraoperative surgical techniques, pharmacologic therapies, as well as transfusion strategies are needed to control the bleeding commonly occurring during HT.

**Topic 6: Documentation and Communication with the Multidisciplinary Team**

**Multidisciplinary Team**
A HT center should identify a multidisciplinary team (composed of individuals from surgery, medicine, nursing, nutrition, social services, physical therapy, and pharmacology) with each member having specific responsibilities. In addition to cardiology and cardiac surgery, medical specialties that should be represented in the cardiac transplant team include infectious diseases, nephrology, pulmonary with respiratory therapy support, pathology, immunology, anesthesiology, physical therapy, and rehabilitation medicine. The Organ Procurement and Transplantation Network (OPTN) in the United States, the British Transplant Society (BTS), and the European Society for Organ Transplantation (ESOT) have recommendations for the multi-disciplinary approach to HT.\(^\text{354, 355}\)

As with the evaluation and discussion that accompanies listing a patient for transplantation, a similar approach is useful in dealing with the HT recipient. In addition to physicians and transplant nurse coordinators, the team should include the following:

- a. Social work/social services personnel have a multifunctional and undisputed role in transplant centers.\(^\text{356}\) One important function is the pre-operative screening for psycho-social conditions that might adversely affect recipient outcome, such as depression, and adherence to medical treatment regimens.\(^\text{357, 358}\)
- b. Psychiatry/psychology specialists diagnose psychiatric illnesses, manage pharmacologic therapy,\(^\text{359}\) and identify personality traits that may allow the transplant team to improve the patient’s understanding and adherence to their medical therapy.\(^\text{360, 361}\) Qualified social work counselors often subsume the functions of these specialists.
- c. In the US, clinical pharmacists can play a pivotal role in the management of HT recipients. In European countries, this role is often fulfilled by transplant physicians. There are numerous interactions among medications and between medications and food and other nutritional supplements requiring both monitoring and education of patients and caregivers on the complexities of pharmacological therapy in HT recipients. These patients often have other chronic diseases, and management of a complex poly-pharmacy is crucial for long-term allograft and patient survival. In the outpatient management of kidney transplant recipients, the involvement of a transplant pharmacist led to improved patient compliance with medications at the end of 1 year (95.1% in those patients who interacted with pharmacists vs. 81.6% with those who did not).\(^\text{362, 363}\) In addition, the inclusion of pharmacy input led to an increase in “therapeutic” drug concentrations from 48% to 64%.\(^\text{363}\)
- d. Dieticians play an important during both the pre- and post-HT periods. Pre-operatively, HT recipients are often malnourished and cachectic as a consequence of long-standing heart failure. Better nutrition at this point improves operative survival. Post-operatively, HT recipients often need education on avoidance of weight gain associated with the use of CSs and hyperglycemia control. Weight loss while waiting for HT is often necessary because obesity in the HT recipient is associated with poorer short-term outcomes.
- e. Physical and occupational therapy are equally important in the pre- and post-HT periods. Cardiac rehabilitation should begin in the hospital and continue after discharge. Supervised exercise may also facilitate adherence to a long-term exercise program.
- f. Infectious disease specialists with a focus on immunocompromised patients are invaluable in the
management of HT recipients in terms of diagnosis and therapy of community acquired and opportunistic infections and the development of protocols for infection prophylaxis against invasive fungi and CMV.

g. In those countries without a socialized or national medical system, financial counselors should be part of the multidisciplinary team to help HT candidates or recipients with insurance claims and health care coverage or private fund raising.

Communication

Meetings should be scheduled at regular intervals to facilitate discussion of HT candidates, recipients, and programmatic concerns. Telecommunication or electronic conferencing can be used to allow for collaborations between geographically distant groups. These meetings should include scheduled internal quality assessments by physicians, nurses, and the other allied health professionals.364

Recommendations for the Documentation and Communication with the Multidisciplinary Team356, 357, 362:

Class I:
1. Transplant centers must have a multidisciplinary approach to patient management.
   
   Level of Evidence: C.

2. The HT team should have regularly scheduled meetings of all disciplines involved.
   
   Level of Evidence: C.

Class IIa:
1. Social work and psychiatry specialists should be integrated into the patient management team.

   Level of Evidence: B.

2. Transplant centers should strive to have specialty-trained pharmacists or physicians with expertise in pharmacology as part of the multidisciplinary team.

   Level of Evidence: B.

Class IIb:
1. Integration of input from pharmacists and infectious disease specialists is important during the development of treatment protocols for HT recipients.

   Level of Evidence: B.

2. Dieticians should be involved in the care of HT recipients to provide input regarding prevention of weight gain and maintenance of glucose control.

   Level of Evidence: C.

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**Topic 7: Use of Extracorporeal Membrane Oxygenation for the Management of Primary Graft Failure in Pediatric Heart Transplant Recipients**

**Primary Heart Allograft Failure**

The ISHLT defines PGF as severe dysfunction of the cardiac allograft in the absence of any anatomic or immunological cause.365 Huang defined it as “circulatory insufficiency within the first 24 hours after HT requiring MCS or the use of 2 inotrope/vasopressor agents.”85 As such, PGF is a diagnosis of exclusion, and reversible causes should be exhaustively sought and corrected prior to making the diagnosis of PGF. This condition accounts for the highest proportion of deaths (20%) in the pediatric population within the first 30 post-operative days.366 In a report from the Pediatric Heart Transplant Study, early heart allograft failure was the commonest cause of early death in infants.367 Finally, mortality due to PGF is higher in recipients with than in those without congenital heart disease (5% vs. 1%), and as high as 10% in infants with hypoplastic left heart syndrome.368 Table 1 summarizes potential causes of PGF after pediatric HT.365

If the recipient cannot be weaned off CPB, MCS should be instituted. Urgent re-transplantation may be considered but it is associated with a high mortality.96, 366, 369

**ECMO and Primary Graft Failure in Pediatric Heart Transplantation**

Since the first reported neonatal survivor in the 1970s, the ECMO portion of the Extracorporeal Life Support Organization (ELSO) Registry contains a total of 386 ECMO therapies for pediatric HT with survival ranging from 31% in newborns to 57% in older children.370, 371 Registry indications for ECMO after HT include pulmonary disease and acute rejection. Requirements for ECMO support in pediatric HT recipients range between 10% and 60% and subsequent survival after PGF varies between 20% and 75%. Some favorable outcomes have been achieved with ECMO as a bridge to recovery and this type of support is available at many pediatric HT centers. Using the definition noted above, Huang reported PGF in 33% of pediatric HT recipients, 44% of whom required MCS.85 There was an 18% early mortality rate in the PGF group. Of 4 children with acute HT failure that were supported with ECMO, 2 survived, 1 after re-transplantation.369 Kirschbom reported ECMO support in 9 of 12 children, only 2 of whom (22%) survived.372 Chou reported a 9% ECMO use rates for PGF, including 4 children, 3 of whom survived.373 Fenton reported 15 children (9% of their transplant series) who required ECMO within 6 weeks of HT
and 58% of these survived. Finally, the Denver group reported that 8 of 14 infants (57%) undergoing HT for hypoplastic left heart syndrome required ECMO after HT and were discharged alive. Survivors were likely to be weaned within 84 hours of ECMO support.

**Indications for ECMO Support after Pediatric Heart Transplantation**

**Failure of Separation from Cardiopulmonary Bypass**

If the recipient cannot be weaned from CPB, the standard measures should be instituted after assessment of residual anatomic lesions, ventilatory and pharmacologic support, hematologic and biochemical profile, and fluid status. Once these measures have been optimized and hyperacute rejection has been excluded, then a diagnosis of primary PGF can be made and ECMO support can be considered.

**Inadequate Post-operative Cardiac Function**

Existing or progressively poorer post-operative allograft function, evidence of a low cardiac output, and poor systemic oxygen delivery unresponsive to escalating medical therapy may also warrant consideration of ECMO support in the ICU. Again, all appropriate measures should be undertaken to optimize support and exclude a correctable cause for the poor allograft function as outlined above.

**Cardiac Arrest**

Emergency cannulation for ECMO during cardiac arrest is increasingly common. Many units now have the capability of rapidly putting children on ECMO during a cardiac arrest and survival can be achieved.

**Recommendations on the Indications for Extracorporeal Membrane Oxygenation in Pediatric Heart Transplant Recipients**

(See Table 8)

**Class IIa:**

1. The use of ECMO should be considered when there is failure to separate from CPB after all correctable causes of such failure have been excluded.

   **Level of Evidence: C.**

2. ECMO should be promptly instituted when progressive heart allograft dysfunction occurs post-operatively.

   **Level of Evidence: C.**

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**Table 8** Potential Causes of Primary Graft Failure After Pediatric Heart Transplantation

**Donor Issues**

- Poor donor organ preservation
- Poor donor quality
  - Diminished echocardiographic ejection fraction
  - Requirement for high inotropic support
  - Elevated blood troponin I level
- Prolonged ischemic time
- Large donor (donor-to-recipient weight ratio >2.0)
- Small donor (donor-to-recipient weight ratio <1.0)
- Prolonged donor cardiopulmonary resuscitation times
- Anoxia as cause of death
- Nonidentical blood type
- Donor age

**Recipient Issues**

- Pre-transplantation diagnosis of congenital heart disease
- Previous sternotomy
- Elevated pulmonary vascular resistance
- Pre-transplantation need for extracorporeal membrane oxygenator
- Pre-transplantation need for ventilatory support

Adapted from Huddleston CB, et al.

**Conduct of Cardiac Extracorporeal Membrane Oxygenation**

There are varying practices for the implementation and management of pediatric ECMO support in the post-operative period to achieve the goal of adequate perfusion and oxygen delivery. Peripheral cannulation may diminish blood loss and yet provide adequate drainage and flows in children weighing < 15 kg. Cannulae placed directly into the aorta and the atria may be associated with improved flows but may be less stable. Direct cannulation may be used in the case of hemodynamic instability or technical difficulties. Approaches including cannulation, technique, equipment, flows, monitoring, and anticoagulation are center specific.

**Left Heart Distension on Cardiac Extracorporeal Membrane Oxygenation**

A left-sided vent is not required if cardiac ejection is sufficient to prevent LV over-distension. Distension of the LV will result in increased wall tension, decreased LV perfusion, and ischemia, which may impair the ability to improve heart allograft function. In addition, LV distension may have detrimental effects on pulmonary function. If pulmonary edema develops or LA/LV distension is detected by echocardiography, a vent should be inserted through the pulmonary vein or directly into the left atrium. Alternatively, if the chest wound has been closed, an atrial
septostomy is performed.384, 385 If it is anticipated that a patient will require ECMO after HT, the atrial septum may be fenestrated at the time of implantation.

Recommendations for the Conduct of Extracorporeal Membrane Oxygenation Support in Pediatric Heart Transplant Recipients.382, 384

Class IIa:
1. The amount of circulatory support provided by ECMO should be sufficient to achieve adequate systemic perfusion and oxygen delivery while waiting for the myocardium to recover.
   
   Level of Evidence: C.

2. Left heart distension during ECMO support should be aggressively treated as it will compromise pulmonary function and impede LV recovery.
   
   Level of Evidence: C.

Duration of Support after Heart Transplantation

The purpose of ECMO is to maintain the systemic circulation and end-organ function while investigating the cause of heart allograft failure, and waiting for myocardial recovery. The literature suggests that cardiac recovery can be expected within 3 to 7 days after HT and this time interval is sufficient to assess severity and reversibility of end-organ damage and to consider other options, including weaning of support due to allograft recovery, implantation of a VAD as a bridge to re-transplantation, or treatment withdrawal.85, 96, 369, 372, 375, 386-388

Timing of Discontinuation of Extracorporeal Membrane Oxygenation Support in the Setting of Primary Graft Failure

Weaning ECMO should be considered when there is evidence of improved cardiac function on echocardiography and evidence of ejection in the arterial tree. Case reports support recovery if there are signs of improvement within 3 to 7 days, but primarily within the first 3 days of support.85, 369, 376, 379, 387

Recommendations for the Timing of Discontinuation of Extracorporeal Membrane Oxygenation Support in the Setting of Primary Graft Failure386

Class IIa:
1. Clinical and echocardiographic variables should be serially assessed to determine if myocardial recovery is occurring.
   
   Level of Evidence: C.

2. Objective signs of recovery should lead to weaning and discontinuation of ECMO support.

   Level of Evidence: C.

Class IIb:
1. Lack of objective evidence of myocardial recovery within 3 to 5 days should prompt consideration of either institution of long term MCS as a bridge to recovery or HT or withdrawal of life-sustaining therapy.

   Level of Evidence: C.

Gaps in Evidence:
1. The optimal modality for surveillance of adverse neurological events during ECMO support for PGF is unknown.
2. Optimal infection prophylaxis in the immunosuppressed patient receiving ECMO support for PGF is unknown.
3. Optimal renal-sparing immunosuppression protocol(s) in patient receiving ECMO support for PGF is unknown.
4. The duration of time waiting for recovery of myocardial function in the setting of PGF beyond which recovery is unlikely is unknown.
5. The role of more intermediate and long-term MCS in patients with myocardial recovery insufficient to allow separation from ECMO within 5 to 7 days is unknown.
6. Risk factors for poor outcomes after re-transplantation in ECMO-supported HT recipients are unknown.

ABBREVIATIONS
AAIR = atrium-paced, atrium-sensed, inhibited-rate modulation
ACC = American College of Cardiology
ACEI = angiotensin-converting enzyme inhibitor
ACT = activated clotting time
AF = atrial fibrillation
AFL = atrial flutter
AHA = American Heart Association
AMR = antibody-mediated rejection
aPTT = activated partial thromboplastin time
ATG = anti-thymocyte globulin
ATP = adenosine triphosphate
ATPase = adenosine triphosphatase
ATP = adenosine triphosphate
BTS = British Transplant Society
CABG = coronary artery bypass grafting
CAD = coronary artery disease
CAV = coronary allograft vasculopathy
CDC = complement-dependent cytotoxicity
cGMP = cyclic guanosine monophosphate
CI = cardiac index
CO = cardiac output
CMV = cytomegalovirus
CNI = calcineurin inhibitor
CPB = cardiopulmonary bypass
CS = corticosteroid
CVP = central venous pressure
CYA = cyclosporine
DDDR = dual-paced, dual-sensed, dual-response to sensing, rate modulation
D/R ratio = donor to recipient ratio
ECG = electrocardiogram
ECMO = extracorporeal membrane oxygenation
ELSO = Extracorporeal Life Support Organization
ESC = European Society of Cardiology
ESOT = European Society for Organ Transplantation
FDA = Food and Drug Administration
FFP = fresh frozen plasma
HIPA = heparin-induced platelet aggregation
HIT = heparin-induced thrombocytopenia
HLA = human leukocyte antigen
HRS = Heart Rhythm Society
HT = heart transplant
IABP = intraaortic balloon pump
ICU = intensive care unit
Ig = immunoglobulin
iNO = inhaled nitric oxide
INR = international normalized ratio
ISHLT = International Society for Heart and Lung Transplantation
IV = intravenous
IV Ig = intravenous immunoglobulin
LV = left ventricle
LVEF = left ventricular ejection fraction
LVH = left ventricular hypertrophy
MCS = mechanical circulatory support
MMF = mycophenolate mofetil
MPAP = mean pulmonary artery pressure
MR = mitral regurgitation
OPTN = Organ Procurement and Transplantation Network
PA = pulmonary artery
PAWP = pulmonary artery wedge pressure
PCC = prothrombin complex concentrate
PGE1 = prostaglandin E1
PGF = primary graft failure
PP = plasmapheresis
PRA = panel reactive antibody
PT = prothrombin time
PVR = pulmonary vascular resistance
RAP = right atrial pressure
rFVIIa = recombinant active factor VII
RV = right ventricle
RVSW = right ventricular stroke work
RVSWI = right ventricular stroke work index
sCr = serum creatinine
SIRS = systemic inflammatory response syndrome
TAC = tacrolimus
TEE = transesophageal echocardiography
t-PA = tissue plasminogen activator
TPG = transpulmonary gradient
TR = tricuspid regurgitation
TRALI = transfusion-related acute lung injury
TVA = tricuspid valve annuloplasty
TVR = tricuspid valve replacement
TTE = transthoracic echocardiogram
UNOS = United Network for Organ Sharing
VAD = ventricular assist device
V/Q = ventilation/perfusion
VT = ventricular tachycardia

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