Management of the Posttransplant Cardiac Patient

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Introduction

The incidence and prevalence of heart failure is increasing at epidemic proportions. The only curative therapy for end-stage heart failure is orthotopic heart transplantation (OHT). Each year, more than 2000 Americans receive cardiac transplantation and this therapy is limited by donor organ supply. With a limited number of organs, donor and recipient are carefully matched, and attention is focused on limiting any complications during the posttransplant period in order to preserve graft function.

This chapter addresses issues pertaining to early graft function, periprocedural immunosuppression, infection prophylaxis, and allograft-related right ventricular dysfunction. These issues that occur during the early period following transplantation are managed by a highly trained and collaborative multidisciplinary health-care transplant team. The key to a successful outcome is measured in all the details surrounding the cardiac transplantation procedure.

The Multispecialist Health-Care Team

Every successful cardiac transplant program offers a highly coordinated team of health-care workers all focused on one common goal. This team includes the cardiac transplant surgeon, transplant cardiologist, the patient's nurse, transplant coordinator, social worker, pharmacist, psychologist, subspecialists (pulmonologist, neurologist, infectious disease specialist, gastroenterologist, etc.), a financial coordinator, dietician, chaplain, and a physical therapist (Fig. 29.1). All of the clinicians and members of the health-care team have tremendous expertise in the care of the transplant patient and the immunosuppressed patient. Everyone involved has important duties that span the pretransplant phase, the transplant procedure, and the posttransplant phase. Collectively, this health-care team provides a high standard of quality care that is required for optimal outcomes.

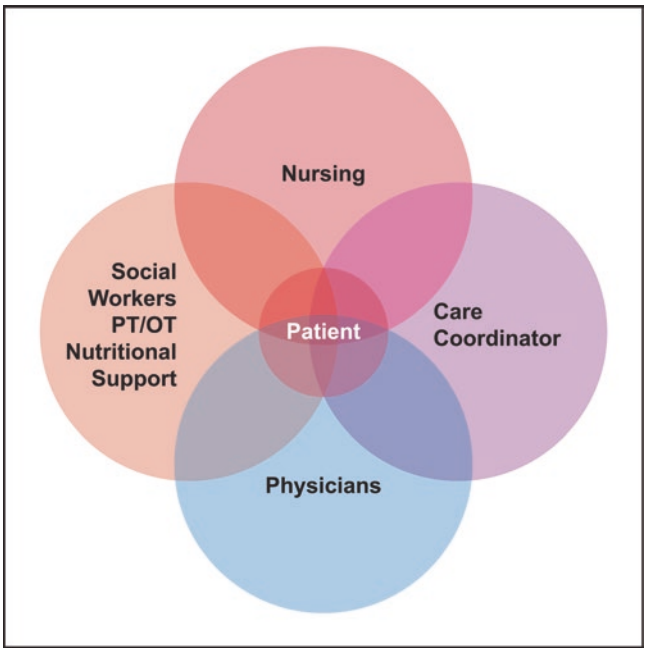


Fig. 29.1 A successful cardiac transplant program requires an integrated team of experts. Venn diagram highlighting the interaction of a multidisciplinary team to deliver care to posttransplant patients

Donor Organ Availability

Each year, about 2200 cardiac transplant procedures are performed in adult US patients. This limited number of transplants is due to a limited number of donor organs. Despite campaigns to increase donor volume, supply has remained flat. A recent study suggests there may be a larger number of organs available for transplant. Data from the US Organ Procurement and Transplantation Network of all potential adult heart donors from 1995 to 2010 revealed more than 82,000 potential donor hearts [1, 2]. About 34% of these donor hearts were accepted, 48% were rejected, and 18% were used for research purposes [3].

The large number of rejected "marginal" hearts is an opportunity for new technologies to boost availability of viable organs. For example, new organ preservation technologies such as "heart in a box" (TransMedics, Inc.) have recently emerged as options that may increase donor organ numbers. TransMedics' Organ Care System is a warm preservation device that provides a clinical platform for ex vivo human heart perfusion and may help preserve function and decrease the ischemic period, resulting in the use of a greater number of donor organs [4]. The PROCEED II (Randomized Study of Organ Care System Cardiac for Preservation of Donated Hearts for Eventual Transplantation) trial demonstrated non-inferiority of ex vivo preservation to cold ischemia. Further, three heart transplant cases in Australian hospitals used organs after cardiac death due to benefits offered by the Organ Care System [5]. Developing new technologies should ultimately facilitate the use of every viable donor organ.

Recipient Issues Affecting Early Postoperative Care

The transplant recipient may present factors that will impact the success of the cardiac transplant procedure. These factors include comorbid conditions such as diabetes mellitus, peripheral vascular disease, chronic kidney disease, pulmonary dysfunction, pulmonary hypertension, obesity, and cachexia. Additional issues include the urgency of transplantation, such as from hemodynamic instability requiring an intra-aortic balloon pump or the need for parenteral inotropic therapy, or presence of ventricular arrhythmias or need for ventilatory support, prior cardiothoracic surgical procedures, and the overall nutritional, emotional, and physical status, (such as frailty) at the time of transplant [6, 7].

In recent years, an increased number of patients with advanced heart failure (and awaiting cardiac transplantation) were supported by mechanical circulatory support devices. The International Society for Heart and Lung Transplantation reported that 19.1 % of cardiac transplant recipients were bridged with mechanical circulatory support in 2000. This number increased to 41.2 % in 2012 [8]. While this field is rapidly evolving with the introduction of new generations of devices, it has also been marked by increased waiting periods for transplant candidates. Moreover, patients supported by mechanical circulatory support typically have longer ischemic periods during the cardiac transplant procedure and have higher panel-reactive antibodies (PRAs) due to a history of blood transfusions, typically at the time of left ventricular assist device (LVAD) implantation [9, 10].

Donor Issues Affecting Early Postoperative Care

Donor biological factors also have a significant impact on the immediate postoperative care of a transplant recipient. Donor-recipient matching in heart transplantation is a multifaceted process. Factors such as age, donor-recipient size matching, cardiac function, preexisting cardiac abnormalities, infection, tissue histocompatibility, and ischemic time for the graft can all affect surgical outcomes. In an era where donor availability is scarce, with increased wait list times, waiting for the "perfect" donor is not a viable strategy. Matching the donor to recipient needs to be individualized on a case-to-case basis.

Donor-Recipient Size Matching

Donor-recipient size matching has resulted in an inconsistent impact on posttransplant survival [11–14]. Sizing considerations for organ allocation currently focuses mainly on body weight, assuming a direct correlation between body weight and cardiac size [15–18]. In one of the largest analyses to date, Patel and colleagues evaluated heart size matching for more than 15,000 recipients and did not demonstrate a 5-year mortality benefit from body weight size matching [16].

Despite these results, guidelines have recommended the following:

1. A heart from a donor whose body weight is less than 30 % of the recipient is acceptable.
2. A male donor with an average weight of 70 kg can be considered for any recipient size regardless of weight [19].
3. Heart size varies by sex. Reduced survival has been shown with donor organ sex mismatch, particularly for male recipients of female organs [15, 18, 20, 21]. As such, caution is advised with female donors whose weight is 20 % lower than that of a male. (4) Undersizing of donor hearts appears to correlate with increased filling pressures [22].

Data suggest that cardiac output in undersized hearts is maintained by elevated filling pressures and tachycardia [22]. Although undersized hearts appear to adapt following transplantation, they frequently are associated with significantly elevated filling pressures in the early postoperative period, which increases the risk of right ventricular and renal failure [23]. Monitoring the use of an undersized donor organ is predicated on the maintenance of optimal filling pressures via the management of volume and the use of inotropes and vasodilators. Depending on the hemodynamic profile, milrinone, nitroprusside, and epinephrine may be useful in alleviating congestion and improving cardiac output.

Severe pulmonary artery hypertension (PAH) is a contraindication for orthotopic heart transplantation. PAH is defined as irreversible pulmonary vascular resistance (PVR) >5 or transpulmonary gradient (TPG) exceeding 15 mmHg [24–26]. PAH in the OHT patient is associated with postoperative right ventricular failure and high morbidity and mortality in the postoperative period. In the setting of mild-moderate preoperative PAH, oversizing is believed to be beneficial in recipients, but this concept is controversial and not universally supported [26, 27]. Patel et al. reported on the association of higher mortality rates with undersized hearts as compared with oversized hearts in the setting of high PVR (>4 Wood units) in the postoperative setting [16]. Costanzo-Nordin and colleagues observed that oversizing was negatively associated with survival irrespective of transpulmonary gradient [27]. Oversizing can delay chest closure and can lead to increased filling pressures and right ventricular failure. Unlike undersized hearts, which adapt, the oversized heart has anatomic constriction, which in the worst cases can only be alleviated with retransplantation or mechanical circulatory support.

The current method of matching size is frequently debated since weight does not represent an accurate and universal assessment of appropriate heart size [20]. Echocardiographic assessment of dimensions, volume, and mass may provide a more accurate assessment of donor-recipient matching.

Donor Age

No set criteria define an age cutoff for donor heart selection. However, older donor age has been identified as a risk factor for all-cause mortality and early graft failure [19]. Advanced donor age is likely associated with a decline in myocardial reserve and the reduced ability to withstand an episode of primary graft failure or acute rejection. Guidelines suggest a donor less than 45 years of age as ideal. Donors between ages 45 and 55 can be used when the ischemic time is less than 4 h, and the use of donor hearts older than 55 years are reserved for recipients whose survival benefit of heart transplantation exceeds the up-front increase in early mortality (extended donor criteria) [19].

Cause of Death

The cause of death of the donor can confer increased risks of mortality for the recipient. For example, donors with brain death commonly have left ventricular (LV) dysfunction, which may or may not improve during the posttransplant period. This LV dysfunction associated with brain death resembles stress-mediated cardiomyopathy. Moreover, left ventricular hypertrophy (especially in the setting of a longer allograft ischemic period) and obstructive coronary artery disease (CAD) of the donor heart can contribute to a worse outcome during and after the transplant. In addition, a donor history of diabetes mellitus is associated with a worse recipient outcome.

Donor Infection

While chronic infections such as human immunodeficiency virus (HIV) and hepatitis C result in a worse recipient outcome, overall, the risk of donor-to-recipient infection transmission is low. However, potential transmission of mediators of endotoxins and infection resulting in donor sepsis may contribute to myocardial dysfunction. Donor hearts deemed low risk for infection transmission are based on the following: (1) donor infection is community acquired, (2) repeat blood cultures prior to procurement are negative, (3) the donor had received pathogen-directed antimicrobial therapy, (4) the donor's myocardial function is normal, and (5) no evidence of endocarditis is present by direct inspection [19, 29].

Drug Toxicities in Donor Hearts

Cocaine: The cardiotoxic effects of cocaine include endothelial dysfunction, vasoconstriction, and direct toxicity resulting in a cardiomyopathy [30]. Intravenous cocaine has an increased incidence of cardiotoxicity and the use of hearts in this scenario is not advised. Based on data from the United Network for Organ Sharing (UNOS), remote cocaine use (less than 6 months) appears to have limited cardiotoxicity, and the donor organ is relatively safe with respect to early postoperative cardiac function. Donor hearts with past or current nonintravenous cocaine abuse can be used for cardiac transplantation, provided cardiac function is normal and left ventricular hypertrophy is absent [30].

Ethanol Abuse: The impact of a donor's alcohol abuse on graft function following transplantation is controversial. Direct toxic effects may result in changes in energy stores—reducing the efficiency of calcium uptake by the sarcoplasmic reticulum, the impairment of sodium-potassium ATPase, and interference with calcium-troponin binding [19, 31]. Therefore, transplantation of a heart with a donor history of alcohol abuse may unmask myocardial biochemical abnormalities and present as early graft failure. The transplant team will have to weigh the potential benefit to the recipient with a heart from a donor who had a history of alcohol abuse.

Carbon Monoxide Poisoning: Carbon monoxide poisoning causes a leftward shift in the oxygen-hemoglobin dissociation curve, reduced oxygen delivery to the tissues, and dysfunction of the mitochondrial cellular respiration [32]. The myocardium becomes particularly susceptible to oxygen deprivation and may manifest as primary graft failure in the postoperative period [32]. Reports of outcomes linked to donors with carbon monoxide poisoning are variable with mixed results [33, 34]. Clinicians should be aware that, despite donors with carbon monoxide poisoning having normal cardiac function based on ejection fraction, there may be a higher incidence of primary graft failure [35, 36]. In cases of carbon monoxide poisoning, the acceptability of donor hearts should be based on all of the following: a normal electrocardiogram and echocardiogram, minimal elevation of cardiac enzymes, minimal inotropic support, short ischemic time, a favorable donor-to-recipient weight ratio, and a recipient with normal pulmonary vascular resistance.

Extended Criteria of Donor Heart

Ongoing debates occur about offering a "marginal donor" heart to a patient who may be a borderline heart transplant candidate, such as an elderly patient or a younger patient with significant comorbidities [37]. Table 29.1 lists the extended donor criteria. Survival outcomes are mixed regarding the use of marginal donor hearts, with some reports of similar outcomes and others reporting worse outcomes—up to 20 % worse than non-marginal heart recipients at 5 years [38–41]. In a retrospective analysis, Schumer and colleagues examined the differences in wait list survival of patients with continuous-flow left ventricular assist devices (CF-LVADs) and posttransplant survival of patients receiving marginal donor hearts. No significant difference in survival was shown up to 2 years follow-up between the two groups [42]. However, survival is worse when comparing recipients of marginal donors' organs to optimal donor organ recipients [42].

Table 29.1 Proposed extended donor criteria for borderline heart transplant recipients

Extended donor criteria
• Donor age > 55
• Hepatitis C positive
• Ejection fraction <45 %
• Requirement for high inotropic support
• Undersized organ mismatch >30 %
• Single vessel coronary artery disease
• Substance abuse (long-term alcohol or cocaine abuse)
• Death by poisoning (carbon monoxide, cyanide)
• Malignant brain tumor
• Long-standing diabetes mellitus
• Prolonged ischemic time

Perioperative Immunosuppression

Protocols for immunosuppression in the perioperative period vary from institution to institution. Preoperative regimens typically include preoperative glucocorticoids and a cell cycle inhibitor. Data from the Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients (OPTN/SRTR) show that the most common regimen in the early postoperative period includes a glucocorticoid, tacrolimus, and mycophenolate mofetil [43]. The benefit of induction therapy remains debated, but about half of US cardiac transplant centers continue to use it [19, 43]. The protocol at the University of Minnesota for cardiac transplantation is outlined as follows. Preoperative steroids in preparation for cardiac transplant are a standard part of the perioperative immunosuppression protocol. The University of Minnesota's protocol for methylprednisolone is 1000 mg IV preoperatively, then 500 mg IV at the release of cross clamp, and then 125 mg intravenous every 8 h (3 doses) starting 12 h postoperatively. Prednisone therapy (1 mg/kg, given in two divided doses) is initiated after completion of the methylprednisolone, tapered (5 mg total per day) until 20 mg po BID, and then tapered by 5 mg after each normal biopsy to 5 mg daily.

In the event of preexisting renal dysfunction, induction therapy with basiliximab may be used to delay initiating a calcineurin inhibitor (CNI). At the University of Minnesota, we use a CNI-delaying protocol for patients with impaired renal function (i.e., creatinine $\geq$1.6 or glomerular filtration rate (GFR) < 30) at the time of transplant and/or posttransplant renal dysfunction. Commonly used agents include thymoglobulin and basiliximab. Thymoglobulin is a polyclonal immunoglobulin mixture raised in rabbits against T lymphocytes (dosing 0.5–1.5 mg/kg IV daily). Dose adjustment is based on CD3 counts, platelet count, and absolute lymphocyte numbers. Thymoglobulin may be used as induction therapy, particularly in sensitized patients and those with a positive B-cell crossmatch, or if renal dysfunction occurs after transplant. Thymoglobulin may be used daily until there is an improvement in renal function. Basiliximab is a chimeric anti-interleukin-2 (IL-2) receptor monoclonal antibody with an initial dose 20 mg given IV day 0 followed by a second dose 20 mg IV on post-op day 4 [44].

Currently, tacrolimus is the most commonly used calcineurin inhibitor during the first posttransplant year [43, 45]. At the University of Minnesota, tacrolimus is the most commonly used CNI and it is typically initiated on postoperative day 1, pending normal renal function. If the renal function is normal and there are no infectious complications, then the target 12-h trough level is approximately 10–15 mg/l immediately posttransplant. Cyclosporine, the alternative CNI, has a target trough level of about 250 ng/ml [43]. Mycophenolate mofetil (MMF) is the preferred cell cycle inhibitor and has been previously shown to be superior to azathioprine in reducing mortality and rejection, although infections were shown to be more common [46]. MMF is given preoperatively at the University of Minnesota (1500 mg po as a single dose) and is subsequently initiated immediately following surgery at 2–3 g IV/PO QD in two divided doses [43].

Bacterial Infection Prophylaxis

Bacterial infections remain a major cause of morbidity and mortality within the first 2 months following cardiac transplantation, with the highest risk in the first week after transplantation [19]. Preventing infection is critical for optimal outcomes and increased patient survival. Strict handwashing before and after patient examination is essential and is the cornerstone of prevention.

Perioperative prophylactic antibiotics include intravenous cefazolin (2 g IV 1 h prior to incision and then 1 g IV every 2 h while patient is in surgery for patient's weight less than 120 kg) or vancomycin (1 g IV 1 h prior to surgical incision then 1 g IV every 8 h while patient is in the operating room with the first dose 8 h after the preoperative dose; the vancomycin should not be given if the creatinine clearance is less than 50 ml/min). Vancomycin is administered in place of cefazolin if the patient is allergic to cephalosporins, has a history of MRSA, or has a history of an anaphylactic reaction to penicillin. Postoperatively, cefazolin (1 g IV every 6 h) is administered for 48 h. For those patients unable to receive cefazolin, vancomycin (1 g every 12 h) is administered for 48 h.

Viral, Fungal Infection Prophylaxis

Cytomegalovirus (CMV) infection, even subclinical, is associated with cardiac allograft vasculopathy and poor outcomes. Prophylaxis has been associated with decreased risk of vasculopathy [47, 48]. For this reason, CMV monitoring and prophylaxis are essential components of posttransplant management. CMV prophylaxis should be initiated within 24–48 h posttransplant. Donor-positive and recipient-negative CMV serology represents the highest risk for the development of CMV-related infections and requires prophylaxis. In addition, at the University of Minnesota, prophylaxis is provided for either donor- or recipient-positive serology (Tables 29.2 and 29.3).

The management of recipients who have negative CMV serology and donor-negative serology is unclear, with some centers electing to administer acyclovir. ISHLT guidelines suggest intravenous ganciclovir postoperatively for high-risk patients [19]. Valganciclovir is an acceptable alternative as its bioavailability is comparable to intravenous ganciclovir and is tenfold higher than that of oral ganciclovir, although it is associated with a greater incidence of leukopenia [49]. It is comparable to oral ganciclovir in preventing CMV infection [50]. Low-risk patients may be considered for preemptive therapy, as they are monitored for nucleic acid or CMV antigenemia assay, and only receive acyclovir for anti-herpes simplex prophylaxis [19] (Table 29.4).

Table 29.2 Recommendations for the prevention of cytomegalovirus in heart transplant recipients (CMV, cytomegalovirus)

Donor serostatus (CMV IgG)	Recipient serostatus (CMV IgG)	CMV risk category	Viral prophylaxis
Neg	Neg	Low risk	Acyclovir 400 mg PO BID ×3 months
Neg	Pos	Moderate risk	Valganciclovir 900 mg PO daily ×3 months
Pos	Pos		
Pos	Neg	High risk	Valganciclovir 900 mg PO daily ×6 months

Table 29.3 Recommended dose adjustments for valganciclovir therapy based on creatinine clearance for cytomegalovirus prophylaxis

Creatinine clearance (ml/min)	Valganciclovir maintenance dose
≥ 60	900 mg QD
40–59	450 mg QD
25–39	450 mg every 2 days
10–24	450 mg twice weekly
Dialysis	Consider IV ganciclovir

Table 29.4 Garding criteria for cellular rejection in heart transplant recipients

Grade		
2004	1990	Histopathological findings
OR	0	No rejection
1R	1A	Focal perivascular and/or interstitial infiltration without myocyte damage
	1B	Multifocal infiltrate with myocyte damage
	2	Diffuse infiltration without necrosis
2R	3A	One focus of infiltrate with associated myocyte damage
3R	3B	Diffuse infiltrate with myocyte damage
	4	Diffuse, polymorphous infiltrate with extensive myocyte damage ±edema, ±hemorrhage, +vasculitis

Antifungal prophylaxis to prevent mucocutaneous candidiasis should be initiated with nystatin or clotrimazole lozenges post extubation. *Pneumocystis jirovecii* pneumonia and *Toxoplasmosis gondii* prophylaxis should also be initiated. Trimethoprim (TMP)/sulfamethoxazole (800–160 mg, one tablet twice weekly) is the standard prophylactic therapy. In the setting of sulfa allergy or glucose-6-phosphate dehydrogenase deficiency, alternative regimens include aerosolized pentamidine, dapsone with or without TMP or pyrimethamine, atovaquone, or clindamycin and pyrimethamine.

Evaluation and Treatment of Early Coagulopathies

Patients with multiple sternotomies, congestive hepatopathy, and those on warfarin therapy are at increased risk for bleeding complications. Platelets and fresh frozen plasma, as directed by the surgical team, are administered as needed. Vitamin K (IV) should be considered preoperatively in high-risk patients—with lower doses preferred compared to higher doses secondary to increased risk of anaphylaxis [19, 51]. Aprotinin, a bovine serine protease inhibitor with antifibrinolytic and anti-inflammatory properties, can reduce bleeding during heart transplantation [52, 53]. However, an observational study showed an increased incidence of end-organ dysfunction, including myocardial infarction, stroke, and renal failure leading to recommendations against its routine use [54].

Tranexamic acid and epsilon-aminocaproic acid also have antifibrinolytic activity that may be considered in high-risk patients to reduce the risk of bleeding before cardiopulmonary bypass. Neither agent has been found to be associated with increased end-organ dysfunction [19, 52, 55]. Recombinant factor VIIa interacts with tissue factor and activates the coagulation cascade. In situations of life-threatening bleeding, recombinant factor VIIa can also be considered [19, 56, 57]. Overall, increased intraoperative use of blood products has been associated with decreased recipient survival at 1 and 5 years posttransplant.

Right Ventricular Dysfunction and Pulmonary Vascular Hypertension Following Heart Transplantation

Despite significant improvements in heart transplant outcomes, right ventricular (RV) failure or dysfunction remains a challenge during the postoperative period. Typically, RV failure after transplant occurs in the setting of preexisting pulmonary hypertension. An increased transpulmonary gradient (greater than 15 mmHg) or a fixed pulmonary vascular resistance greater than 5 Wood units has been associated with an increased 30-day mortality post cardiac transplantation. Moreover, a linear relationship exists between PVR and mortality [58]. Early recognition and preemptive use of pulmonary vasodilators may be beneficial.

In the setting of RV failure due to pulmonary hypertension, pulmonary vasodilators such as sildenafil, nitric oxide, and epoprostenol may improve RV afterload [59–63]. Inotropic support may also be useful as preload optimization, maintenance of sinus rhythm, atrioventricular synchrony, and optimization of ventilator support [19, 64]. Inotropic support agents that augment right ventricular performance include isoproterenol, milrinone, dobutamine, and epinephrine [65]. Atrial and ventricular temporary epicardial pacing support should be used to maintain heart rates greater than 90 beats/min postoperatively [19, 64]. If there is no response to inotropic and pulmonary vasodilator therapy, or if progressive end-organ dysfunction occurs, consideration should be given to mechanical circulatory support.

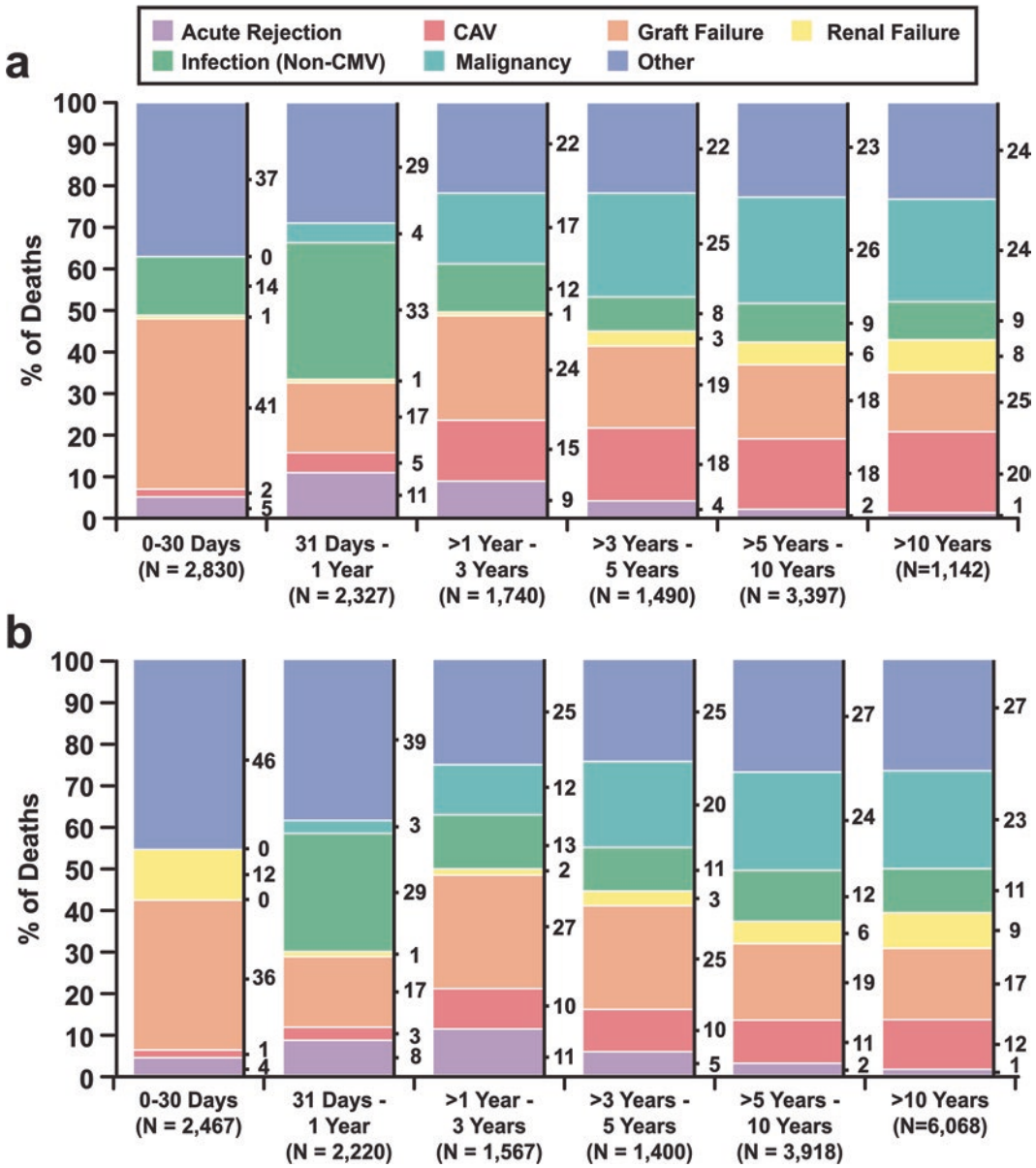
Immune and Rejection Monitoring

The challenge of finding the delicate balance between rejection and infection begins immediately after transplant. The risk of cellular rejection is highest in the first year following a

heart transplant. Heart transplant recipients with preexisting antibodies are particularly challenging due to their increased risk of rejection and mortality after transplant [66]. Furthermore, de novo antibodies can develop, placing a patient at increased risk for rejection in the early posttransplant period.

Monitoring for rejection should include the measurement of donor-specific antibodies and early biopsy for cellular and antibody-mediated rejection (AMR) (i.e., within 10 days following cardiac transplantation). The criteria for pathologic AMR were recently defined and suggestions made for monitoring intervals [19, 67, 68]. AMR should be evaluated using either immunohistochemical assays for C4d and C3d immunofluorescence.

Measurement and interpretation of donor-specific antibodies have been limited due to the lack of standardization. In addition, the management of donor-specific antibodies (DSAs) in the absence of graft dysfunction or evidence of rejection on biopsy is unclear. However, DSAs are associated with poor survival and cardiac allograft vasculopathy [68–70]. The majority of de novo DSAs appear to be anti-HLA-DR and anti-HLA-DQ [68–70]. The use of solid-phase assays has enabled the identification of HLA antibodies and their strength. New techniques, such as the C1q assay provide assessment of complement fixation, which will further define the antibodies that are clinically relevant, at least in the short term. ◘ Figures 29.2 and 29.3 illustrate the leading causes of death stratified by era and time of death.



◘ **Fig. 29.2** Causes of death for cardiac transplant recipients. (**a**) Highlights causes of death for adult cardiac transplant recipients from 1994 to 2001. (**b**) Highlights causes of death for adult cardiac transplant recipients from 2002 to 2012 (Data adapted from J Heart Lung Transplant. 2014;(32)10. Thirtieth Official Adult Heart Transplant Report—2013)

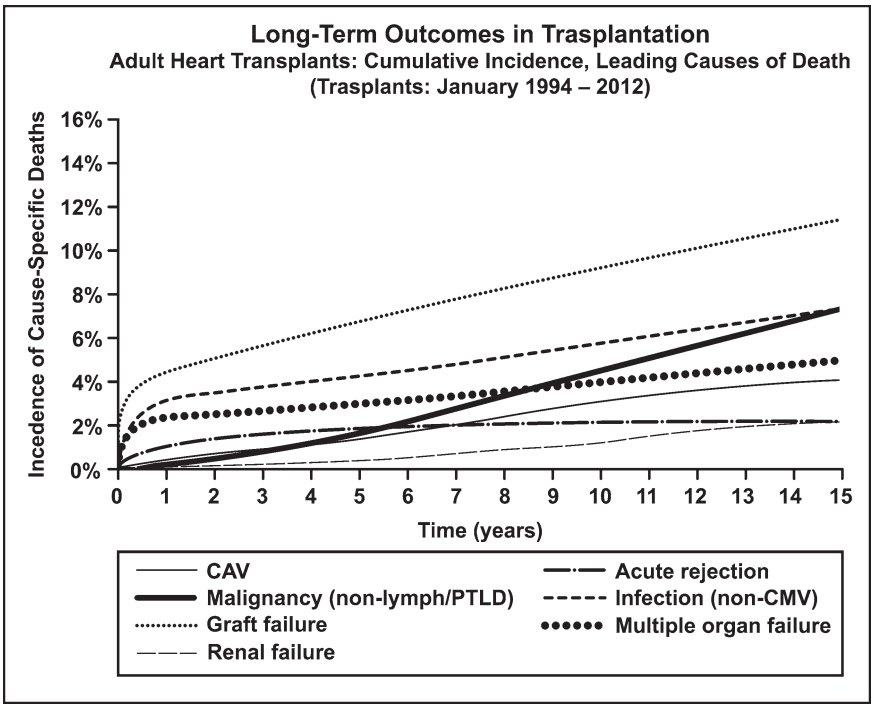


Fig. 29.3 Graft failure is the leading cause of death following heart transplantation. Data highlighting the leading causes of death following cardiac transplantation from 1994 to 2012 (Data adapted from J Heart Lung Transplant. 2014;33(10))

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Managing Sensitization and Positive Crossmatch

As previously emphasized, sensitization is associated with poor outcomes following heart transplantation [66]. Prior to transplantation, desensitization could be performed to reduce the number of HLA antibodies. Desensitization strategies in cardiac transplantation have typically emerged from data based on the management of kidney transplants. A few small, single-center studies have been conducted with heart transplant recipients, and results have been difficult to interpret due to lack of standardization and controls.

Strategies that have incorporated IVIg and plasmapheresis appear to be successful in decreasing antibodies [71]. There are data suggesting rituximab and bortezomib as viable strategies [72, 73]. In our experience at the University of Minnesota, few patients actually respond to these therapies, and a decision has to be made whether to pursue transplantation in this setting. Figure 29.4 outlines our initial algorithm for desensitization. Several strategies may be undertaken in this scenario. Pre-, intra-, and postoperative plasmapheresis may be used to remove circulating antibodies, and the addition of IVIg, thymoglobulin, and/or rituximab may decrease the production of antibodies. Campath has been used in highly sensitized patients undergoing transplant, but it is associated with a high rate of rejection [74]. Close monitoring for rejection after transplant is required.

A positive crossmatch is associated with increased risk of mortality and hyperacute rejection [75, 76]. In a retrospective analysis of recipients who had a positive crossmatch, those who received plasmapheresis had improved survival compared to those who did not receive plasmapheresis [77]. IVIg may abrogate a positive crossmatch and may be considered in this setting. It is typically combined with plasmapheresis [78].

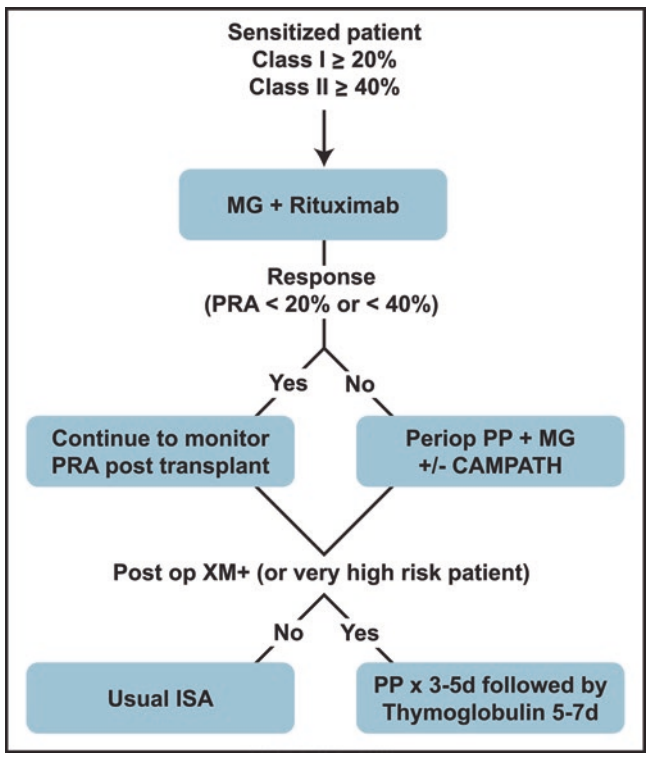

Fig. 29.4 Proposed algorithm for desensitization therapy. Note that desensitization therapies include intravenous immunoglobulin (IVIG) infusion, rituximab, plasmapheresis (PP), Campath (alemtuzumab), and thymoglobulin [postoperative (post op) and crossmatch (XM)]

Summary and Future Initiatives

Survival following cardiac transplantation has improved tremendously over the past several decades. The sustained function of the allograft is multifactorial. The use of a coordinated

health-care team, infection prophylaxis, renal-sparing immunosuppression protocols, and matching strategies to pair the best donor and recipient has collectively impacted the quality of life of the cardiac transplant recipient and their survival. Future initiatives that will further impact survival and graft function following cardiac transplantation will include personalized immunosuppression modifications, the development and use of donor risk scores, the development of new immunosuppressive agents that have limited organ toxicity profiles, and improved organ preservation systems (e.g., heart-in-a-box technology). The ability to use all available donor organs for cardiac transplantation will have an enormous impact on the field and save lives.

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