

BRIEF REVIEW

# Cardiac Transplantation for the Practicing Clinical Cardiologist

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Since the advent of immunosuppressive therapy, orthotopic heart transplant has emerged as a widely accepted therapeutic option for end-stage heart disease. As the number of transplantations increase, it is very likely that cardiologists not formally trained in transplantation will participate in the care of patients listed for transplant as well as those patients who are post-transplant. In fact, it is common practice for the transplant cardiologist and referring cardiologist/inter- nist to share management duties and responsibilities for this population of patients. In this regard, the transplant patient may present a unique and challenging opportunity for the nontransplant physician. This overview will focus on the referral for transplantation, as well as the treatment principles encompassing today's cardiac transplant patient.

## Referral for Transplantation

The indications and contraindications for cardiac transplantation are outlined in Tables 1 and 2, respectively. These criteria serve as rough guidelines for the transplant team and should by no means be considered concrete. Many of the contraindications are "correctable", and thereby may allow a larger number of patients to be considered for transplant.

The transplant evaluation includes a comprehensive history and physical examination; hematological and chemical analysis of blood; urinalysis and 24-hour urine collection for protein and creatinine clearance; chest X-ray; pulmonary function tests with diffusion testing; malignancy screening as appropriate; cardiovascular evaluation (electrocardiogram [ECG], echocardiogram, right heart catheterization evaluating pulmonary vascular resistance, left heart catheterization evaluating coronary artery and bypass patency, cardiopulmonary stress testing with measured aerobic capacity); financial, social, and psychiatric consultations; serologic screening (ABO/Rho, human immunodeficiency virus (HIV), hepatitis, cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex, tuberculosis); and immunologic evaluation. Basically four questions need to be answered:

1. Does the patient have adequate financial resources to cover the procedure, and the long-term cost of immunosuppression?
2. Is the cardiovascular disease severe enough to warrant transplantation?
3. Is the patient otherwise well enough to withstand the transplant surgery and subsequent immunosuppression?
4. Is this a patient who will be able to comply with the long-term demanding medical program required for successful organ transplantation?

If the answer is yes to these four questions, the patient most likely is a transplant candidate.

After satisfactory completion of the pretransplant evaluation, the patient is then "listed". Listing is currently performed on a regional and national basis. The list is based on ABO blood type, body weight, time-on-list, and clinical status. Status 1 listing is reserved for those patients dependent on chemical or mechanical inotropic support for survival. Status 2 is for all other patients, regardless of inpatient admission. Unfortunately, due to the large demand for cardiac transplantation and the paucity of donor organs, status 2 patients now wait >200 days for an organ. With this knowledge, referral for cardiac transplantation should be considered earlier in the patient's treatment course. Once an organ does become available, the recipient is notified and asked to come to the hospital within 4 hours. Again, due to the organ shortage, most of the patients transplanted today are status 1 and are already in the hospital.

## The Immediate Transplantation Procedure

Simply described, the diseased native heart is explanted by cutting through both atria, the aorta, and main pulmonary artery. The allograft atria are trimmed leaving a small cuff which can be sewn to the remaining native atria. Care is

Table 1. INDICATIONS FOR CARDIAC TRANSPLANTATION

Maximum oxygen consumption during exercise <14 ml O <sub>2</sub> /kg/min
Severe myocardial ischemia not amenable to revascularization
Recurrent ventricular arrhythmias refractory to all therapeutic modalities
Persistent or labile fluid imbalance despite tailored medical therapy and compliance

Table 2. CONTRAINDICATIONS TO CARDIAC TRANSPLANTATION

History of emotional instability, medical noncompliance, or active substance abuse (includes cigarettes)
Fixed pulmonary hypertension (varies from ≥2 to 4 RU among programs)
Significant cerebrovascular disease
Active malignancy or life-limiting coexisting illness
Physiologic age >60-65 (varies with program)
Significant peripheral vascular disease
Active peptic ulcer disease or diverticular disease
Severe bronchitis or chronic obstructive lung disease
Morbid obesity (>20% excess of ideal body weight)
Sarcoid or amyloid
Irreversible hepatic or renal dysfunction
Recent pulmonary embolus
Severe osteoporosis
Active infection
Diabetes with end-organ dysfunction
Immunologic sensitization

**Table 3. EFFECTS AND SIDE EFFECTS OF IMMUNOSUPPRESSIVE MEDICATIONS**

Medication	Mode of Action	Side Effects	Drug Interactions		
			Increases Concentration	Decreases Concentration	Increases Toxicity
Cyclosporine	Block secretion of IL-2	Hypertension Renal Failure Neurotoxicity Hirsutism	Erythromycin Ketoconazole Diltiazem Barbiturates Amiodarone Coumadin	Dilantin Phenobarbital Rifampin	NSAID's Amiodarone
Steroids	Lymphocytic agent	Diabetes Hypertension Osteoporosis Cataracts	None	None	None
Azathioprine	Purine antimetabolite	Leukopenia Pancreatitis Transaminitis	None	Allopurinol	Allopurinol
Mycophenolate	Inhibits purine synthesis, B and T cell proliferation	GI distress Infections Leukopenia	Acyclovir Ganciclovir	Antacids Cholestyramine	Salicylates Probenecid
OKT3	Opsonizes lymphocytes	Allergic reactions Leukopenia Serum sickness	None	None	None

IL-2 = interleukin-2; NSAIDs = non-steroidal anti-inflammatory drugs; GI = gastrointestinal.

taken to not damage the allograft sinus node. The pulmonary and aortic arteries are then anastomosed. The initial hospitalization for the transplant patient is approximately 10–14 days. The acute perioperative mortality rate is 14% for the more ill status 1 patients and 6% with status 2 recipients. Nearly all of these early deaths are due to primary graft failure or infectious complications (1).

Patients, once discharged from hospital, are lodged in a local apartment for another 4 weeks during which time they receive intensive physical therapy. Also, for the first six weeks, patients undergo weekly endomyocardial biopsies as a screen for graft rejection, and adjustments in the immunosuppressive medications. Once released, patients are usually able to return to a high level of activity with significant improvement in quality-of-life scores.

**New Heart, New Medicines, New problems**

With the joy and elation of receiving a new heart also comes a new list of medicines and medical problems.

*Immunosuppression*

Most patients are discharged on “triple therapy” consisting of anti interleukin (IL)2 agent (cyclosporine, tacrolimus-“FK506”), antilymphocyte antimetabolite (azathioprine, mycophenolate, methotrexate, cytoxan) and corticosteroids. This combination has resulted in an improved patient survival post-transplant and minimized drug side-effects. However, these drugs can be toxic and have multiple drug interactions (Table 3). A careful balance must exist between the

protection afforded by immunosuppressive therapy against allograft rejection and the exposure of the allograft recipient to the serious risk of infections, neoplasm, and hypertension.

*Allograft Rejection*

Among the most important complications of cardiac transplantation is acute allograft rejection. Despite optimal immunosuppression, on an average, patients have 1.8 episodes of cellular rejection. Most episodes occur in the first 3 months after transplantation, with a decreasing incidence throughout the first year. Less frequent is rejection beyond 1 year. Late cellular rejection usually occurs within one month after an infection and is thought to be a result of immune system activation. Risk for rejection includes female donor-male recipient, presence of preformed antibodies, very young or very old, and acute infection (2). Usually rejection is asymptomatic early in its course (hence the reason for surveillance biopsies), but in more advanced stages, patients may present with dysrhythmias, congestive heart failure or fatigue.

Given the likelihood of rejection, an accurate assessment of allograft rejection is necessary. Endomyocardial biopsy remains the gold standard for diagnosing acute allograft rejection. Billingham developed a grading system based on the histological severity of the sample and standardized the histological nomenclature to reduce intraobserver variability (3). This grading scale (Table 4) assists in the long-term follow-up of transplanted patients, as well as monitoring of improvement in rejection episodes.

Endomyocardial biopsy has its own limitations, such as

**Table 4. STANDARDIZED CARDIAC BIOPSY GRADING**

Grade	Histologic Description
0	No rejection
1A	Focal, mild lymphocytic infiltrate without myocyte necrosis
1B	Diffuse, mild lymphocytic infiltrate without myocyte necrosis
2	One focus of aggressive lymphocytic infiltration and/or focal myocyte damage
3A	Multiple aggressive areas of lymphocytic infiltration and/or myocyte damage
3B	Diffuse inflammatory process with borderline severe myocyte necrosis
4	Diffuse aggressive lymphocytic infiltrate, edema, hemorrhage, and vasculitis with myocyte necrosis

forceps-induced artifact and sampling error. Rejection, therefore, may occur "in the absence" of histological evidence. Patients with allograft dysfunction but with no histological evidence of cellular rejection are presumed to have humoral rejection. It is characterized histologically by immunoglobulin deposition and activated endothelial cells in the absence of cellular infiltrate. Humoral rejection is most common in the first month and it has an extremely poor prognosis.

#### *Treatment of Acute Allograft Rejection*

Specific therapy for acute allograft rejection depends on the hemodynamic status of the transplanted allograft, the histologic type and severity of the rejection, current and previous immunosuppressive regimens, and the time since transplantation. Most transplant cardiologists agree with treating grade 3 and 4 rejection. Grade 2 rejection often regresses on its own and therefore is not uniformly treated. Grade 1 rejection is not usually treated. Most episodes of rejection can be treated with a short pulse of higher dose corticosteroids. However, more severe rejection requires OKT3, immunopheresis, or total lymphoid irradiation.

#### *Cardiac Allograft Vasculopathy*

The major limitation to long term survival for the cardiac transplant recipient has been the development of obstructive coronary artery disease or cardiac allograft vasculopathy. The disease is presumed to be of immunologic basis, although other factors such as CMV infection and hyperlipidemia also appear to correlate with the development of allograft vasculopathy. Due to cardiac afferent denervation at the time of surgery, rarely do typical anginal symptoms suggesting obstructive coronary artery disease arise.

The most common coronary lesion is a diffuse gradual narrowing that involves the entire length of the artery with obliteration of the smaller distal branch vessels. Focal stenotic lesions and angiographically-apparent collateral circulation are less commonly seen. Severe diffuse coronary disease is often found at the time of autopsy in many patients who had "normal coronary angiograms" only a few months

prior to their death. Due to the insensitivity of the coronary angiogram, intravascular ultrasound and coronary flow reserve are promising invasive techniques which may more accurately predict coronary events.

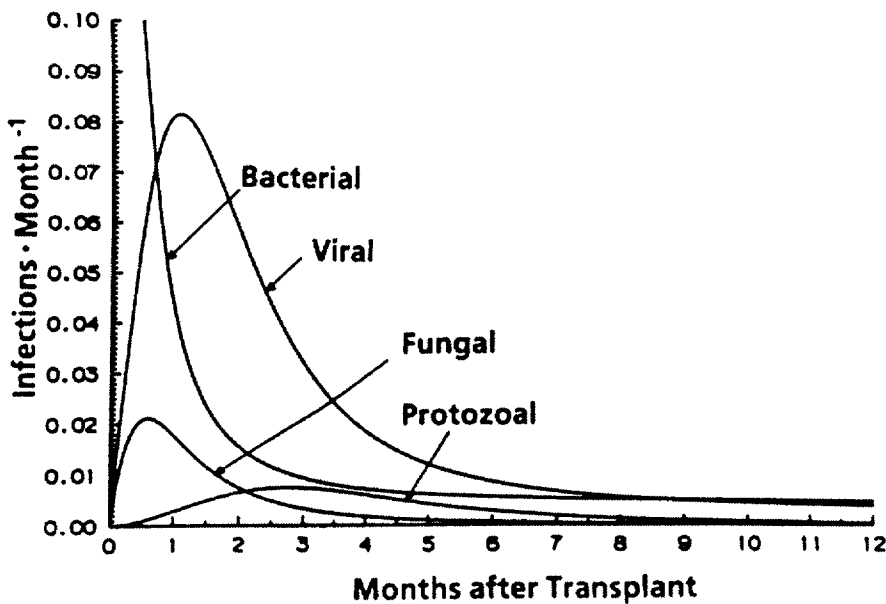
Prophylactic use of diltiazem early in the posttransplant course appears to diminish the incidence of cardiac allograft vasculopathy angiographically (4). Although the exact mechanism is not fully understood, it appears to inhibit immune-mediated injury and its associated rapid coronary intimal proliferation. Other mechanisms involving the regulation of lipoprotein-receptor synthesis, uptake/degradation of lipoprotein, cholesterol-ester hydrolytic activity, or arterial-matrix synthesis may also contribute (4). A number of studies have demonstrated the direct antiatherosclerotic effect of calcium antagonists in animal models, but studies are lacking in the transplant recipient. Long-term follow-up to determine the clinical benefits of diltiazem await further trails. Newer immunosuppressive regimens utilizing tacrolimus (FK506), mycophenolate mofetil, and rapamycin which inhibit smooth muscle proliferation may offer hope in the future.

Survival rates for those transplant recipients with a 70% stenosis of one major coronary artery vessel is approximately 60% at two years, and only 20% at six months if three vessels are involved. When found, focal lesions can often be approached with percutaneous revascularization techniques. Post-intervention results are similar to those reported in nontransplant coronary arteries (5). Restenosis remains a common complication and long-term benefits of mechanical revascularization remain to be seen.

#### *Infection*

Although the incidence of posttransplant infection has decreased, infection remains a major cause of posttransplant morbidity and mortality in the cardiac transplant recipient. There seems to be a bimodal peak of infection frequency (6) (Figure 1). One occurs in the first month posttransplant and is usually related to nosocomial infections. The second period, one to five months posttransplant, is overwhelmingly dominated by opportunistic infections such as CMV, pneumocystis, and fungal infections. Community-acquired bacterial infections tend to predominate long-term follow-up. A recent review of 814 patients from the Cardiac Transplant Research Database Group (6) found the incidence of serious infections to be 0.5/patient during a mean follow-up period of 8.2 months. Bacteria accounted for 47%, viruses for 41% and fungi and protozoa combined for the remaining 12% of infections. Overall mortality was 13% per infectious event. Bacterial infections, and sometimes CMV, tend to manifest quickly (in <24–48 hours) while a gradual or subclinical onset is typical of a viral infection. The lung is the most commonly infected site followed by the blood, urine, gastrointestinal tract, and sternum.

The most common single infectious agent following car-



**Figure 1.** The risk of first-time infection of each major category of infectious agents is shown plotted against time since transplant. Note the early peak in bacterial infections (most all nosocomial) with a later "second" peak of opportunistic viral, fungal, and protozoal infections. Figure reproduced with permission from Miller LW, Naftel DC, Bourge RC, et al. Infection after heart transplantation: a multiinstitutional study. *J Heart Lung Transplant* 1994;13:381-93.

diac transplantation is CMV. It usually occurs 4 to 8 weeks posttransplantation and may manifest as a primary infection, reactivation, and/or superinfection. Primary CMV infection may occur in the seronegative recipient who acquires a seropositive allograft, but it may also be acquired from transfused blood products. Reactivation may occur in the seropositive patient due to viral replication posttransplant. Primary infection usually causes a more serious infectious course than does reactivation. The clinical presentation of CMV infections is widely variable and can present as anything from an asymptomatic rise in antibody titer, to life threatening multi-organ system failure. CMV has been associated with an increase in opportunistic infections, accelerated atherosclerosis in the transplant recipient and acute allograft rejection (7). Any suspicion of CMV infection should include an early aggressive diagnostic approach to allow for immediate treatment. Gancyclovir has been shown to be a highly effective therapy against CMV infections. In the life-threatening disease state CMV-specific hyperimmune globulin or pooled immunoglobulins may enhance the antiviral therapy. Concomitant superinfections, especially pneumocystis, in the immunocompromised patient should always be investigated in the CMV-infected transplant recipient. Prophylactic administration of Gancyclovir in a large, multicenter, randomized double-blind study demonstrated a significant reduction in the incidence of CMV disease compared to placebo (8). Immunization with a live attenuated strain of CMV in seronegative candidates and use of immunoglobulins to prevent CMV infection in transplant recipients may also play an important role in the future prevention of CMV infections.

*Hypertension*

Hypertension is an extremely common phenomenon in the posttransplant patient. In the precyclosporine era, the incidence of hypertension was only 20%, but since the introduction of cyclosporine >75% of all cardiac transplant recipients develop significant hypertension. It is independent of race, gender, age, prior history of hypertension and is relatively common in the pediatric recipient. Although the exact mechanism remains unknown, cyclosporine-associated hypertension is associated with a sodium-avid state, volume expansion, alteration of intracellular calcium-ion regulation, the production of excess vasoconstrictive prostaglandins, increased sympathetic tone and a lack of the normal nocturnal decrease in blood pressure (9). Treatment of posttransplant hypertension can be difficult and should include dietary restriction of salt intake, along with calcium channel blockers and angiotensin converting enzyme (ACE)-inhibitors as first line agents. The most frequently used calcium channel blocker is diltiazem because of its cyclosporine-sparing effects and its potentially beneficial effects on cardiac allograft vasculopathy. ACE-inhibitors should be used with caution because of their potential for renal toxicity and hyperkalemia in combination with cyclosporine. Combination therapy is often necessary. Due to a dependence on circulating catecholamines to maintain heart rate and blood pressure, beta-blockers should be used with extreme caution. The long-term benefit of antihypertensive control in the cardiac allograft is yet to be fully understood.

*Hyperlipidemia*

Hyperlipidemia is a very common entity in the cardiac transplant recipient, occurring as often as 60 to 80%. The

increase occurs as early as 2 to 3 weeks posttransplant and is associated with an increase in low density lipoprotein and triglycerides. Allograft recipients with prior ischemic heart disease have a much greater incidence of hyperlipidemia compared to those with idiopathic cardiomyopathy. The magnitude of total cholesterol increase from pretransplant ranges from 30 to 80 mg/dl, and the greatest increases seem to occur in those patients with no prior history of hyperlipidemia (10). Obesity and cumulative corticosteroid dosing appear to strongly correlate with the high incidence of elevated lipids in the cardiac transplant population. Other proposed mechanisms suggest that severe congestive heart failure in the pretransplant period may alter gastrointestinal absorption, increase passive liver congestion and not allow for an accurate assessment of lipid profiles in the pretransplant era. Weight loss, low-fat diet, smoking cessation, and exercise are nonpharmacologic measures that should be encouraged in all patients. If these non-drug interventions prove to be inadequate after 6 months, then pharmacologic therapy should be instituted. Hydroxy-methyl-gluteryl coenzyme-A (HMG-CoA) reductase inhibitors are the preferred agent of choice at many transplant centers. These agents should be used with care due to the risk of myositis and transaminase increase. Aggressive lowering of lipids in the hyperlipidemic transplant population also decreases the development of cardiac allograft vasculopathy, improves survival, and may decrease the risk of rejection (11, 12).

#### Malignancy

The risk of developing malignancy after cardiac transplantation is approximately 5%, or 100 times higher than that of the general population. With the overall increase in survival, it is anticipated that the prevalence of malignancy will increase as well. The development of carcinoma appears to be a side-effect of long-term immunosuppressive therapy. Skin cancers (basal cell and squamous cell carcinomas), the most common associated malignancy, are thought to arise from the azathioprine metabolite, nitromidazole. This metabolite causes significant photosensitivity increasing the susceptibility to cutaneous neoplasms. Patients are advised to avoid prolonged exposure to sunlight, use adequate skin protection, and avoid known carcinogens such as tobacco products. Early detection and surgical excision allow for cure.

Lymphoproliferative disorder in transplant recipients receiving cyclosporine is thought to result from unregulated EBV-driven B-cell proliferation. The peak incidence occurs 12 to 18 months posttransplant with disease progression correlating with the intensity of the immunosuppressive regimen. Treatment options include reduction of immunosuppression, chemotherapy, radiation therapy, and high dose acyclovir; however, mortality remains high.

#### Conclusion

Cardiac transplantation offers improved survival and quality-of-life for patients with end-stage heart disease. With the growing population of transplant recipients, it is very likely that cardiologists not trained in transplantation will participate in the care of these patients. The standard will be regular continuing care at home with ongoing communication with the transplant center. Therefore, an understanding of "normal" and possible complications following cardiac transplantation is crucial. Understanding the dynamic world of cardiac transplantation is not simple, but its potential rewards extend beyond the realms of medicine.

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