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Primary Panel: Heather Ross (Co-Chair), Paul Hendry (Co-Chair), Anne Dipchand, Nadia Giannetti, Greg Hirsch, Debra Isaac, Narendra Singh, Lori West, Michel White

Secondary Panel: Andrew Ignaszewski, Anton Maria Chung, Lynn Straatman, Dennis Modry, Wayne Tymchak, Jeffrey Burton, Wayne Warnica, Jose Eduardo Azevedo, William Kostuk, Alan Menkis, Peter Pflugfelder, Mackenzie Quantz, Ross Davies, Henry Haddad, Roy Masters, Robert Cusimano, Diego Delgado, Chris Feindel, Vivek Rao, Marcelo Cantarovich, Renzo Cecere, Michel Carrier, Michel Pellerin, Daniel Doyle, Marie-Hélène LeBlanc, Jonathan Howlett

Alexis Carrell, having perfected techniques of vascular anastomosis, published a report on the successful heterotopic heart transplantation in the dog in 1905 (1). It awaited a better understanding of transplantation biology, forged by Medawar and others in the 1940s, and the development of successful immunosuppressive regimens in renal transplantation in the 1950s for the stage to be set for successful cardiac transplantation. Shumway established a research program in transplantation at Stanford University and published a report with Lower of the first orthotopic canine transplant, using a biatrial anastomotic technique that would be established as the standard approach (2). In 1966, Barnard, a fellow trainee with Shumway at The University of Minnesota in the 1950s, performed the first successful human cardiac transplant at Cape Town, South Africa. There was widespread enthusiasm for the procedure, but this spate of interest declined with poor short term survival. Stanford, however, under the guidance of Shumway steadily improved results through their program of combined research and clinical activities. By the late 1970s, cardiac transplantation was established as an effective therapy for end-stage heart failure, largely through their efforts.

Cardiac transplantation is now the treatment of choice for patients with severe end-stage congestive heart failure (CHF) in whom maximal medical therapy has failed. Improvements over the past few years in organ donation, organ preservation and antirejection therapy have resulted in improved survival rates after heart transplantation (3). However, there is a worldwide gap between the supply of and demand for transplantable organs, and this gap is enlarging. The problem has reached a crisis level in Canada. Of those patients currently on a heart transplant list approximately 50% will never receive a transplant (4). In Canada in 1999 there was a 21% increase in the number of patients listed for heart transplant but only a 6% increase in the number of donors over that same time period (see www.chi.ca), resulting in an annual 25% mortality for those awaiting a transplant. Heart transplant rates in Canada have been steady over the past decade at 160 to 180 per year. This problem exists despite expanding acceptance criteria for donor hearts and using 'marginal' donors. Current listing criteria are extremely strict, and conservative estimates are that only 5% to 10% of those who may benefit from a new heart are receiving a transplant, and this is likely conservative. There may be as many as 5000 patients in Canada younger than 65 years who would benefit from a heart transplant, a number that doubles with every five-year increase in age distribution (4).

TABLE 1
Guidelines on recommendations: Levels of evidence

Grade A recommendation
Level 1 evidence: Large scale randomized trials or meta-analysis with clear-cut results
Grade B recommendation
Level 2 evidence: Small scale randomized trials or meta-analysis with less certain results
Grade C recommendation
Level 3 evidence: Nonrandomized contemporaneous controls
Level 4 evidence: Nonrandomized historical controls
Level 5 evidence: Case series

What are the possible solutions? The first is to increase organ donation. However, even with optimal organ donation, including strategies such as 'presumed consent', use of more marginal donors, and institutional and donor family financial incentives, many believe there will still not be enough organs to meet the need or the demand (4). In fact, the recent report from the International Society of Heart and Lung Transplantation (ISHLT) suggests that despite aggressive measures to improve organ donation, worldwide there has been a decrease in the number of heart transplants performed (3). Improvements in medical therapy continue to reduce disease progression and increase survival for patients with end-stage diseases such as CHF (see www.ccs.ca for guidelines on management of heart failure). However, CHF is a disease generally characterized by inexorable progression, and improvements in medical therapy have not reduced organ transplantation need, only delayed it. Given the frequent insidious onset of pulmonary hypertension, early referral for

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Correspondence: Dr Heather Ross, Divisions of Cardiology and Transplant, Toronto General Hospital, University of Toronto, 10 NU 129-200 Elizabeth Street, Toronto, Ontario M5G 2C4. Telephone 416-340-3482, fax 416-340-4134, e-mail Heather.Ross@uhn.on.ca

and assessment of cardiac transplant is important. Other areas of research in techniques such as stem cells, gene therapy or cellular augmentation and tissue engineering appear promising but are not yet in the clinical arena (4).

The purpose of this consensus document is to outline the indications and contraindications for transplant, to review the surgical management of the recipient and donor, to review post-transplant management including rejection, infection, transplant coronary artery disease (TCAD) and malignancy, and to review potential alternatives to transplantation that are emerging. A standard grading system was used for these consensus recommendations (Table 1).

Currently the expected one-year survival after transplant is 80% (3), though most single-centre reports suggest one-year survival in the 85% to 90% range. There is a relatively constant 4% mortality per year after the first year following transplantation, with an expected five-year survival close to 70%. The mean survival is 9.1 years and the conditional survival for those who survive the first year is 11.6 years (3).

INDICATIONS AND CONTRAINDICATIONS FOR CARDIAC TRANSPLANT

The listing criteria for cardiac transplantation were recently reviewed by the American Society of Transplantation (5), as well as the Canadian Cardiac Transplant Group (6). These criteria are designed to identify patients who are at the greatest risk of dying and who will derive the greatest benefits from cardiac transplantation (5).

Functional class

It is well accepted that patients with advanced symptoms of heart failure (New York Heart Association [NYHA] functional classes III and IV) have a worse outcome than patients with class I and II symptoms. Patients with recent hospitalizations are at particularly high risk of dying from cardiac causes. Functional class can be affected by adjustments in medical therapy and therefore functional class should not be the sole requirement for listing. Functional testing, when feasible based on patient status, must be performed by exercise stress testing with expiratory gas analysis (cardiopulmonary study) to document the degree of limitation. It provides an objective assessment of functional class, is correlated with survival and allows consistency across transplant programs.

In the pediatric population, heart failure may manifest itself in other ways including failure to thrive or growth retardation; as such, patients may not be easily classified by NYHA criteria. Objective functional assessment may not be possible due to patient age or ability to cooperate.

Assessment of functional capacity by respiratory gas analysis

Exercise performance relies on cardiac inotropic and chronotropic reserve, as well as on peripheral vascular and muscular function (7). Exercise testing with gas exchange analysis allows a more accurate assessment of exercise capacity than a standard exercise test. Predicting oxygen uptake (VO_2) based on the treadmill or bicycle ergometer workload alone can be very misleading in patients with CHF (7). In fact, in patients with heart failure, the lack of habituation to the treadmill or bicycle, poor fitness and the disease itself significantly decrease the correlation between predicted (based on workload) and measured VO_2. Exercise testing with gas exchange analysis allows an accurate assessment of cardiopulmonary reserve and confirms that the exercise test is indeed maximal (7).

Although some controversy exists over the degree of impairment in exercise capacity required to justify transplantation, in general, patients with peak VO_2 less than 10 mL/kg/min should be listed for cardiac transplantation (5,7-11). In contrast, patients with a peak VO_2 of 18 mL/kg/min or greater will experience one-year survival rates above 95% (8) and should be followed up expectantly. The management of patients with an intermediate exercise capacity, specifically a VO_2 between 10 and 18 mL/kg/min, remains controversial (8). In fact, since Mancini et al (10) originally published a VO_2 of less than 14 mL/kg/min as an indication for transplantation, other investigators have reported that peak VO_2 data should be analysed in a continuous fashion. Myers et al (8) reported that patients with a VO_2 between 10 and 18 mL/kg/min exhibited a gradually poorer prognosis as the VO_2 decreased, as opposed to a threshold of risk when the maximal VO_2 reached 14. Aaronson et al (12) investigated the prognostic value of peak VO_2 versus the percentage predicted maximal VO_2 based on age and sex (normalized peak VO_2) and found that they were equally good predictors of survival. However, normalized peak VO_2 appeared to yield better prognostic value in women. A blunted systolic blood pressure response to exercise, defined as a systolic blood pressure at peak exercise of 120 mmHg or less and chronotropic incompetence, when associated with a maximal VO_2 less than 15 mL/kg/min and a peak VO_2 less than 50% predicted, helped refine the prognostic value of an intermediate maximal VO_2 value (13).

> **Practical tip:** maximal VO_2 should be interpreted with caution in patients with advanced symptoms who fail to reach their anaerobic threshold (14).

Pulmonary hypertension

Most patients with CHF being considered for heart transplantation have at least moderately elevated pulmonary artery pressures (15,16). Elevated pulmonary vascular resistance (PVR) is an independent risk factor for mortality both early and late after orthotopic heart transplantation (16). The pretransplantation PVR affects post-transplant outcome at both one and five years in a linear fashion. In fact, the odds ratio for increased mortality reaches 1.3 for a PVR of 3 Wood units and 1.5 for a PVR of 4 Wood units at one year. The actual degree of pulmonary hypertension that precludes cardiac transplantation is controversial because there is a continuum of increasing risk as pulmonary pressures rise. It is generally accepted that patients with a PVR of 3 Wood units or more and a transpulmonary gradient (mean pulmonary artery pressure – mean pulmonary capillary wedge pressure) of 12 mmHg or more have significant pulmonary hypertension and an increased risk of dying early after transplantation (5,6,17,18). However, severe and fixed pulmonary hypertension – that is, a pulmonary artery systolic pressure greater than 50 mmHg, PVR greater than 4 Wood units, PVR index greater than 6 Wood units or transpulmonary gradient greater than 15, measured after aggressive challenge with milrinone, sodium nitroprusside or nitric oxide – should be considered to be a contraindication for cardiac transplantation (5,16-19).

Pediatric patients with certain diagnoses with concurrent pulmonary hypertension may remain heart transplant candidates and should be assessed on an individual basis (that is, hypoplastic left heart syndrome, restrictive cardiomyopathy and others).

Neurohormones

Many neurohormones have been associated with adverse outcomes in patients with CHF. Among the most discriminative for predicting adverse outcomes in patients with CHF are plasma noradrenaline (20), endothelin-1 and big endothelin-1 (21), as well as the atrial and brain natriuretic peptides (22,23). Recent publications suggested that big endothelin (21) and both natriuretic peptides (22) may be of value in deciding to list a patient for cardiac transplantation. In fact, plasma big endothelin levels above 4.3 mmol/L have been associated with significantly worse outcomes in patients with advanced disease (22). Specifically, the big endothelin-1 level carried a better predictive value than peak VO_2 in predicting adverse outcomes in patients with advanced heart failure. In another recent report by Isnard et al (22), plasma atrial natriuretic peptide, left ventricular (LV) ejection fraction and plasma noradrenaline but neither peak VO_2 nor percentage or predicted VO_2 were independent predictors of death or transplantation in a cohort of patients with severe symptomatic heart failure. Of all neurohormones, brain natriuretic peptide appears to be the most sensitive hormone to diagnose CHF and to measure the impact of therapy (24-27). At this point, neurohormone measurements are cumbersome, expensive and at the normal values quite variable from one centre and technique to another. Thus, the measurement of such parameters as a routine tool to select candidates for cardiac transplantation is not warranted. The recent development of inexpensive kits to measure plasma brain natriuretic peptide (24,25) that may allow serial measurements in patients with advanced disease appears promising.

Ejection fraction

There is no specific LV ejection fraction that would result in listing for cardiac transplantation. However, it is recognized that the survival decreases in a parallel fashion with the decrease in LV ejection fraction and the increase in LV volume (28). In fact, in a multivariate analysis, Koelling and co-workers (29) reported that advanced age, high resting heart rate and increased LV end-diastolic volume index were independently related to a worse outcome at one year in patients with heart failure referred for cardiac transplantation. A more recent investigation also reported that a restrictive filling pattern is associated with poorer outcomes in patients with CHF (30,31). Right ventricular ejection fraction has also been shown to be an independent risk factor for increased mortality (32-34).

Age

The upper age limit for transplantation has been the subject of lengthy debate. Single-centre data have suggested that outcomes of cardiac transplantation in patients older than 50 years did not differ significantly from outcomes of patients younger than 50 years (35). However, the ISHLT (3) report confirmed a curvilinear impact of increasing recipient age on decreasing survival, the strongest impact being observed in the middle of the sixth decade. Older patients must be in good condition with few relative contraindications and should be screened more aggressively for associated comorbidities. It may not be the recipient age itself that predicts an increased mortality after transplantation but what comes with age.

The option of listing prenatally when the fetus reaches a gestational age of 36 weeks exists.

Re-evaluation

Once listed for transplantation, patients should be re-evaluated. Some patients will improve and they should be considered to be put them on 'hold'. As well, patients who remain stable for at least six months on the transplant list may have a very good prognosis. Patients such as these should have repeat cardiopulmonary testing and be considered for delisting (36,37). Conversely, some patients may develop complications while waiting on the list and no longer be suitable for cardiac transplantation; they should be delisted.

Other indications for transplantation

Patients with severe coronary artery disease (CAD), although it is an uncommon indication for transplantation, may be considered for cardiac transplantation if they experience Canadian Cardiovascular Society class IV symptoms not amenable to high risk revascularization and in whom maximal medical therapy has failed. Patients who have refractory life-threatening arrhythmias that are not amenable to treatment should also be considered for transplantation. In the pediatric population, in addition to LV dysfunction, the major indication for heart transplantation is severe congenital heart disease not amenable to or considered too high risk for surgical palliation.

Contraindications – other

Other relative or absolute contraindications to cardiac transplantation include primary systemic disease that may limit long term survival (hepatic, pulmonary or renal insufficiency not due to prerenal azotemia [creatinine greater than 200 µmol/L]), active infection, psychosocial issues, drug or alcohol abuse and documented noncompliance. All patients should have a minimal period of abstinence from tobacco, alcohol or drugs that may be centre specific but should generally be at least three to six months before patients are considered for listing for transplantation. Recent nonbasal cell malignancy (within five years), morbid obesity (more than 140% ideal body weight) or marked cachexia (less than 60% ideal body weight), osteoporosis, significant cerebral or peripheral vascular disease and diabetes mellitus with evidence of end-organ damage are also considered contraindications.

Occasionally severe chromosomal, neurological or syndrome abnormalities may also be contraindications to pediatric heart transplantation.

1. Recommendations: Indications and contraindications for cardiac transplantation (consensus)

Indications

1. Advanced functional class (NYHA class III to IV);
2. Poor one-year survival: peak VO_2 less than 15 mm/kg/min or 50% or more than predicted for age and sex; peak VO_2 15 mm/kg/min or greater to 18 mm/kg/min or less with refractory angina or life-threatening arrhythmia;
3. Failure to respond to maximal medical therapy;

4. Absence of alternative or conventional surgical options;
5. Absence of contraindications;
6. Potential to undergo rehabilitation after transplantation.

Contraindications – either absolute or relative

1. Pulmonary hypertension after aggressive challenge with one or more vasodilators or inotropic agents and systolic blood pressure above 85 mmHg, transpulmonary gradient greater than 15 mmHg, systolic pulmonary artery pressure greater than 50 mmHg, PVR greater than 4 Wood units, PVR index greater than 6;
2. Primary systemic disease that may limit long term survival (such as hepatic or pulmonary diseases);
3. Renal dysfunction – persistent increase in creatinine above 200 μmol/L after inotropic challenge and adjustment of medications (such as discontinuation of angiotensin-converting enzyme [ACE] inhibitors, adjusted diuretics);
4. Active infection;
5. Technical issues
6. Psychosocial issues: active smoking (three months' abstinence is required); drug or alcohol abuse (at least three months' abstinence is required); unstable or chronic psychiatric conditions (such as multiple suicide attempts); noncompliance (documented life-threatening noncompliance);
7. Recent malignancy (within five years);
8. Morbid obesity (greater than 140% ideal body weight) or marked cachexia (less than 60% ideal body weight);
9. Osteoporosis – patients with bone mineral density more than 2 SD below normal or at high risk;
10. Significant peripheral or cerebrovascular vascular disease;
11. Diabetes mellitus with end-organ damage.

SURGICAL MANAGEMENT OF THE RECIPIENT AND DONOR

Surgical techniques

Bicaval anastomosis: The biatrial technique of orthotopic cardiac transplantation has been the standard approach since its initial description by Lower and Shumway in 1960 (2), and excellent short and long term results have been realized in tens of thousands of patients with this approach. Briefly, this approach uses four separate anastomoses between recipient atria and great vessels (after recipient ventriculectomy) and the atria and great vessels of the donor heart. This technique is well described and illustrated in the literature (38,39). However, variations including bicaval anastomosis were described as early as 1959 (40). Pulmonary vein to pulmonary vein anastomoses were used for domino transplants and to solve anatomical problems related to cardiac tumours or congenital anomalies in the recipient that mandated a more complete recipient atriectomy. There has been renewed enthusiasm for these approaches as an alternative to the biatrial technique in an effort to ameliorate a variety of problems that have been attributed to the biatrial approach. These include conduction disturbances requiring pacemaker placement in 4% to 15% cases (41), risk of thromboembolism, poor atrial synchrony between donor and recipient, and atrioventricular valve regurgitation related to distortion of atrial anatomy (42). The surgical approaches to bicaval and pulmonary vein to pulmonary vein anastomoses are well described in the literature (43).

Retrospective clinical studies overall have shown fewer episodes of tachyarrhythmia, slightly better hemodynamics, less tricuspid regurgitation (44-46) and less need for permanent pacemakers in patients who underwent bicaval versus biatrial anastomosis. There have been variable results on survival with some supporting an improved survival (45) and others showing no difference in mortality (46). As well, the bicaval group had a better exercise tolerance than the biatrial group (45). These studies must be viewed with caution given that they are retrospective and often compare patients from different eras and different degrees of centre experience in transplantation.

Atrial function studies using Doppler echocardiography comparing transmitral flow velocity integrals to determine left atrial transport have been performed. Patients in whom the bicaval/pulmonary vein to pulmonary vein technique had been used had normal left atrial transport, while those who had undergone the biatrial technique had lower late diastolic flow integrals. There were, however, no differences in ventricular performance between the groups (47-49). The significance of the improved atrial function may perhaps become apparent in cases of ventricular diastolic dysfunction. Traversi et al (50) reported similar findings in 22 bicaval and 27 biatrial cases with worse tricuspid regurgitation in the biatrial group (13 of 27) than in the bicaval group (three of 22).

In contrast with the above positive studies, Grande et al (51) compared 46 bicaval with 72 biatrial transplants performed more or less in the same time frame. There were no significant differences between groups with regard to requirement for pacemaker therapy, perioperative arrhythmias, or mitral or tricuspid regurgitation. Brandt and colleagues (52) studied 39 biatrial and 40 bicaval transplants with a minimum of nine months' follow-up. The only difference between groups was a markedly higher rate of atrial arrhythmias in the biatrial group (12 of 39 versus one of 40). There were no differences in hemodynamics, including right atrial pressure, or in pacemaker requirements. One reported complication of bicaval anastomoses is superior vena cava syndrome. Sze et al (53) found only three cases out of 124 bicaval transplants, all treated successfully by percutaneous methods, versus no cases in the 742 patients transplanted with the biatrial technique.

Aziz et al (54) compared 96 bicaval (single left atrial anastomosis) versus 105 biatrial transplants with follow-up to a maximum of 72 months (minimum 12 months) in a randomized trial determined by coin toss at the time of operation. Hemodynamic evaluation early and at 12 months revealed higher right atrial pressure (11 versus 4 mmHg), lower cardiac index (2.5 versus 3.8) and higher mean pulmonary artery pressure (28 versus 22 mmHg) with the biatrial than with the

bicaval approach. Interestingly, LV ejection fraction was better up to two years with the bicaval approach, and moderate and severe grades of tricuspid regurgitation were more common in the biatrial group (35% versus 12% at two years). Actuarial survival at one, three and five years was better in the bicaval group (87% versus 74%, 82% versus 70% and 80% versus 62%, respectively).

Bainbridge et al (55) prospectively randomized 58 consecutive patients to biatrial versus bicaval and pulmonary vein to pulmonary vein anastomoses. There were no significant differences between the biatrial (n=29) and the bicaval (n=29) groups. There were no differences in cardiopulmonary exercise testing or survival. There was more tricuspid regurgitation in the biatrial group (10 or 19 versus three of 22). Arrhythmias and pacemaker requirements were not reported. This was a rather small study and was underpowered to prove the null hypothesis by the absence of a significant difference in survival between groups.

In summary, the preponderance of retrospective data, including Doppler echocardiography studies, indicates a potential benefit related to the bicaval approach. The most consistent finding is improved atrial function that in the setting of normal ventricular diastolic function fails to alter hemodynamics. It is possible that the improved atrial function translates into improved hemodynamics and possibly survival as ventricular diastolic dysfunction occurs over time. There are fairly consistent data that tricuspid regurgitation is reduced with the bicaval approach and that this is sustained over time. There are conflicting data concerning the requirement for pacemaker therapy and atrial arrhythmias, in both the short and long term after transplantation, with the two techniques.

In the pediatric population recipient size, heart location, site, and systemic venous and pulmonary venous anatomy must also be taken into consideration when determining the surgical approach of biatrial versus bicaval.

2. Recommendations: Surgical technique

1. The surgical technique for heart transplantation where technically feasible should be by the bicaval approach (**grade B, level 2**).
2. Data are insufficient to comment on single versus bilateral left atrial anastomoses.

Recipient management

Termination of cardiopulmonary bypass after cardiac transplantation involves the usual skills and techniques that apply to more routine cardiac operations; however, some special considerations apply. Specifically, the acutely denervated heart is frequently in a junctional rhythm and thus atrial pacing, isuprel or both are frequently needed. Some degree of elevated PVR, either fixed or dynamic, is a common condition in recipients with end-stage heart failure. In addition, some degree of right ventricular dysfunction as a result of ischemia-reperfusion injury, and compounded by donor brain death, may be anticipated (56). Management of acute decompensation of the transplanted right ventricle is perhaps the most vexing and life-threatening problem in the early management of these patients. Fifty per cent of complications and 19% of early deaths are attributed to right ventricular failure early (57). There is sufficient centre-to-centre variability in the approaches to acute right ventricular failure that consensus is difficult to obtain. Initially the maintenance of atrial contraction, through either atrial pacing or isuprel infusion (10 to 70 ng/kg/min), is important to aid in filling the acutely decompensated right ventricle. Neither atropine nor neostigmine has been found useful in the transplanted heart (39). Inotropic support by the usual adrenergic agonists is initially used in an effort to improve right ventricular contractility. Assiduous avoidance of hypercapnea (and even the establishment of hypocapnea through hyperventilation) and acidemia will prevent further increases in PVR through vasospasm. Finally, pharmacological attempts to induce pulmonary vasodilation are recommended. A variety of agents have been used including inhaled nitric oxide, intravenous milrinone, prostaglandin E1 and sodium nitroprusside. In a small randomized trial, Rajek and colleagues (58) treated transplant patients with either prostaglandin E1 or inhaled nitric oxide (n=34 each). The nitric oxide-treated group had better reduction in PVR with less reduction in systemic vascular resistance, and nitric oxide was more effective in facilitating weaning from cardiopulmonary bypass. Pagano et al (59) found that nitric oxide compared with intravenous prostaglandin E1 was more effective in reducing PVR with no effect on systemic vascular resistance. Intra-aortic balloon counterpulsation may be useful in the management of patients with acute right ventricular failure. Arafa and colleagues reported on a small series of five patients managed with intra-aortic balloon counterpulsation, with early reduction in transpulmonary gradient and long term survival in four patients.

3. Recommendation: Recipient management

1. For patients with elevated PVR strategies to lower PVR should be used including inhaled nitric oxide, milrinone and prostaglandin E1 in facilitating successful weaning from cardiopulmonary bypass (**consensus**).

Donor issues

General: In Canada, as in most countries performing transplantation, the rate of organ donation is insufficient to meet the increasing demand. Therefore, it is necessary to put special emphasis on increasing organ procurement activity. Paradoxically, the scientific community gives much less attention to organ procurement and preservation than to organ transplantation. Certainly, both processes are essential and are mutually dependent on one another. The main step to improve procurement and transplant activity is through education. This activity must be aimed at different levels including the general public and health care professionals.

An ongoing training program for health care professionals should be present in every medical institution to improve the identification and management of potential donors. Dedicated intensive care unit teams with standardized protocols to identify and maintain donors may increase donor rates. Responsibility must be shared among federal and provincial governments, private and public organisations, medical institutions, individual professionals and the general public to improve donation and transplantation in Canada.

During the early stages of organ procurement, a substantial number of donors are lost because they are not identified. Steps must be put in place to improve the overall procurement system. A method to rapidly determine brain death, a process to

obtain family consent and aggressive medical management of the potential donor must be implemented to increase organ donation rates.

Two processes take place during brain death: first, autonomic storm and second, dysfunction of the hypothalamic-hypophyseal axis with subsequent abnormal circulating hormonal levels. The adrenergic storm can induce a significant increase in systemic vascular resistance, reducing peripheral perfusion and producing definitive organ failure if medical interventions are unable to stop the process in time. Another consequence may be hypertension, which acutely increases myocardial wall stress, resulting in subendocardial ischemia. These hemodynamic changes can lead to LV dysfunction and low cardiac output and loss of potential organs.

Technique of cardiectomy: The technique of donor cardiectomy, including salient points regarding intraoperative assessment of the donor heart, is well described in several illustrated manuals (38,61). With the popularization of bicaval anastomoses there is a need for increased mobilization, and resection of the superior vena cava and, to a lesser degree, the inferior vena cava. Specifically, the superior vena cava should be transected above the level of the azygos vein and the inferior vena cava at the diaphragm (62). A collaborative approach between procurement teams for liver, heart and lungs is mandatory for the well-being of all potential recipients involved.

In some complex congenital heart disease there may be a need to include significant portions of branch pulmonary arteries, aorta, vena cava or the innominate vein to facilitate the anastomosis within the recipient (that is, hypoplastic or absent central pulmonary arteries, dextrocardia with left superior vena cava, isomerism with left inferior vena cava and others). This may potentially affect the use of other organs, especially the lungs.

Donor criteria: The limited number of donor hearts relative to patients queued for cardiac transplantation places pressure on the transplant team to accept hearts that are older, that require significant inotropic support and that are less than ideally size matched – the so-called 'marginal' donor.

Older donors: Drinkwater and colleagues (63) have reported on the use of older donor hearts, a large proportion of which are used at the University of California Los Angeles for older recipients within an alternate transplant list pioneered there. They report a one-year survival of 79% in a cohort of 52 patients (mean age 56 years) with hearts from donors older than 45 years (mean 51 years). Ten patients required concomitant coronary artery bypass and had a one-year survival of 60%. The authors used angiography in the older donor hearts whenever there was a family history or donor history suggestive of CAD (63). Pflugfelder et al (64) reported on 219 transplants from a single centre with donor age range from 10 to 50 years, and by univariate analysis could not detect any risk related to donor age. Nevertheless, multicentre registries have identified older donors as an independent risk factor for poor outcome (3). The ISHLT registry data accorded donor age 50 an odds ratio for one and five year mortality of 1.4 and 1.38, respectively, and donor age above 65 an odds ratio of 1.81 at one year and 1.77 at five years (3). Hearts from older donors are at particular risk for CAD, as well as reduced compliance, dependence on atrial contraction and reduced responsiveness to adrenergic stimulation (65).

Prolonged ischemic times: Ischemic times over 4 h, using current organ preservation techniques, have been shown in multi-institutional studies to be a risk factor for reduced short and long term survival (66). Furthermore, prolonged ischemic times act synergistically with other risk factors such as older donor age to worsen outcomes (67). More recent single-centre reports indicate that prolonged ischemic times (range 71 to 441 min) did not adversely effect either short or long term outcomes (68). Novel approaches to organ preservation hold the promise for reducing the impact of increased ischemic times as a risk factor for poor outcomes (see below). Ischemic times longer than 4 h have been reported in pediatric heart transplantation without adversely affecting short or long term outcomes.

Donor heart dysfunction: Diffuse wall motion abnormalities on echocardiography have been reported as an independent risk factor for adverse outcome in a multicentre study (69). Wheeldon et al (70) reported on a standardized aggressive approach to donor management including Swan-Ganz catheters, onsite resuscitation with a cardiac anaesthetist and tri-iodothyronine therapy. They reported excellent results, with 44 of 52 initially unacceptable donor hearts used with acceptable short and long term survival. Jeevandandam and colleagues (71) have also reported salutary effects of tri-iodothyronine therapy on donor myocardial dysfunction. Kron and colleagues (72) reported excellent results from a single institution with 11 marginal cardiac donors with marked improvement in ejection fraction in the early postoperative period.

4. Recommendations: Donors

1. Increasing donor age is associated with increased risk of TCAD and poorer short and long term survival. Donors older than 50 years should be carefully selected, including coronary angiography where indicated (**grade C, level 3**).
2. Donor ischemic times should be less than 4 h because ischemic times longer than 4 h remain a risk factor for adverse short and long term outcomes. Prolonged ischemic times should be assessed on an individual basis (**grade C, level 3**).
3. Marginal donors due to high dose inotropes and diffuse wall motion abnormalities should be assessed individually with aggressive onsite resuscitation of the donor by the procurement team (**grade C, level 3**).

Donor heart allocation: Blood group O is the universal donor and AB the universal recipient. Given that a blood group O donor can be allocated widely but a blood group O recipient can receive only a blood group O donor there is often a critical shortage of organs for O recipients. Hearts are also size matched between the donor and recipient (donor range 0.8 to 1.2 recipients based on body surface area). As such, a large – for example 110 kg – O recipient may wait a substantially longer time on the list than a small– for example 50 kg – A recipient.

Hearts are also allocated according to a status system, with the patients at highest risk and therefore greatest need taking priority. In Canada consensus was reached on a priority allocation system with patients who are mechanically assisted (ventilation, intra-aortic balloon pump, ventricular assist device [VAD]) and intensive care unit, coronary intensive care unit

or cardiac care unit dependent taking the highest priority (status 4). Patients on high dose single or multiple inotropes are also recognized to be at high risk of dying and are considered status 3b. Patients who have a VAD in place but are not intensive care unit or cardiac care unit dependent are high status but at a lower risk than inotrope-dependent patients and therefore are status 3a. Next on the priority list are patients requiring hospitalization (status 2), followed by patients at home (status 1). Patients who have been accepted for transplantation and develop intercurrent issues are put on hold (status 0).

As such, hearts are allocated according to status, blood group, body size and, finally, time on a waiting list.

IMMUNOSUPPRESSIVE THERAPY

Prevention

Panel reactive antibody (PRA) is screened in patients before transplantation in an effort to minimize the risk of allograft rejection after transplantation. PRA tests for the presence of preformed human lymphocyte antigen (HLA) antibodies to a random panel of donor lymphocytes. High PRA titres (higher than 10%) are associated with an increased incidence of rejection and reduced survival after cardiac transplantation (73,74). Females, patients with history of multiple blood transfusions or prior transplant, and patients on VADs are at increased risk for high PRA titres (75). There are various strategies to try to lower PRA in sensitized patients, including plasmapheresis with administration of intravenous immunoglobulin G immediately before transplantation or while on cardiopulmonary bypass (76).

Donors and recipients are matched for ABO compatibility but because of the scarcity of donor organs and timing issues surrounding transplantation, prospective HLA matching is not routinely performed before transplantation. In patients with a high PRA, prospective direct donor and recipient T cell crossmatches may be done before transplantation; however, this requires time and in general is only feasible with a local donor. A prospective final crossmatch may not be necessary in patients deemed nonsensitized (low PRA) by highly sensitive testing in an effort to reduce cold ischemic time (77,78).

The goal of post-transplant immunosuppressive therapy is to prevent the occurrence of allograft rejection while minimizing toxicity and infectious and malignant complications. There is still much controversy over what constitutes the optimum immunosuppressive regimen for the cardiac transplant recipient. The only clear agreement is that within the concept of low intensity immunosuppressive therapy there must be room for flexibility and individualized approaches, according to each centre's clinical expertise (79).

Patients with complex congenital heart disease with previous palliative surgery are most at risk for increased PRA. Ideally in this group prospective HLA donor- and recipient-specific crossmatching should be carried out. Though the majority of pediatric patients undergo ABO matched transplants, infants less than one year of age have successfully undergone ABO-incompatible heart transplantation with acceptable outcomes as part of a research protocol.

Induction therapy

Induction therapy was introduced in an effort to reduce steroid use and nephrotoxicity associated with early high dose calcineurin inhibitor use while minimizing episodes of rejection. It involves short term use immediately after transplantation (days 0 to 7, until therapeutic levels of calcineurin inhibitor are reached) of an intensive anti-T cell regimen. Intravenous steroids followed by tapered steroid doses are used (see Steroids section). There are various induction protocols involving the use of either polyclonal or monoclonal antibodies. Polyclonal antibody induction therapy (for example, ALG, ATG, ATGAM, RATG) has been shown to be effective in both prophylaxis and treatment of rejection (80). Unfortunately, polyclonal agents have antibodies to B cells and nonlymphoid cells, as well as to the intended T cell population. This global suppression can lead to an increased incidence of opportunistic infections and therefore more specific induction agents have been sought and developed.

OKT3 is a monoclonal antibody directed specifically against the T cell, in an effort to reduce T cell-mediated cellular immunity while sparing the rest of the host's immune system. While OKT3 has demonstrated efficacy when used to treat steroid resistant rejection, it has several adverse effects that limit its utility as a widespread induction therapy. It can result in massive cytokine release and is associated with significant immunogenicity. This latter effect may preclude its later use for treatment of rejection in some patients (81,82). OKT3 use has been associated with an increase risk of infections and post-transplant lymphoproliferative disorder (PTLD), especially at higher doses (83,84).

Monoclonal antibodies are being developed that are targeted to highly specific, key components of the rejection pathway that will reduce rejection while leaving the remainder of the host's immune system intact, therefore avoiding excessive infections and malignancy. Possible candidates include antibodies directed against T cell subsets such as CD4+ and CD25+ cells, various adhesion and costimulatory molecules, and cytokine receptors. The use of recombinant DNA technology has allowed the 'humanization' of murine and rat antibodies, leading to fewer adverse effects and immunogenicity with these preparations. The most highly developed at this time are humanized monoclonal antibodies directed toward the interleukin (IL) -2 receptor. Basiliximab (Simulect) and daclizumab (Zenapax) specifically bind the IL-2 receptor and have been shown in small scale clinical trials to be effective in reducing early rejection in cardiac and noncardiac allograft recipients (85-88).

Whether induction therapy is necessary or advantageous overall in cardiac transplantation remains controversial, with many single-centre retrospective studies showing both negative and positive outcomes. Myriad agents, dosages, protocols and combinations with other immunosuppressive agents have been used as induction therapy, making definitive comparisons and recommendations difficult. Because of this, the use of induction therapy and the specific agents used have been site specific and dependent on clinical experience and preferences of individual transplant programs.

The following arguments in favour of induction therapy are based primarily on data on polyclonal antibodies:

1. *Ability to protect patients with renal and hepatic dysfunction from adverse effects of early calcineurin use*. This may allow renal recovery in cardiac transplant patients with prerenal kidney dysfunction without the negative impact of high dose cyclosporin or tacrolimus early after transplantation (89,90). Hepatic recovery may also be expedited in this way (91).

2. *Ability to reduce rejection in high risk recipients*, such as multiparous women, crossmatch-positive recipients, HLA-sensitized recipients or patients undergoing retransplantation (92,93). It has been suggested that patients with a high risk of late rejection should be given induction therapy with polyclonal antibody.
3. *Reduction of intensity of immunosuppressive therapy over the long term*. A comparatively lower steroid requirement when induction therapy is used is potentially advantageous for diabetics with refractory hyperglycemia or patients with postoperative bacterial infections. There has been some evidence that recurrent episodes of rejection are more readily reversed with steroid boluses alone (without the need for OKT3) in patients who have received polyclonal induction therapy (94). Studies have also suggested that patients receiving induction therapy can be weaned off steroids and have a rejection incidence comparable with those on triple immunosuppressive therapy (95). Improved steroid resistant rejection-free rates are reported when induction therapy is used in combination with both tacrolimus- and cyclosporin-based regimens (96). It is unclear whether these findings translate into significantly improved patient survival in the longer term.

Arguments against the routine use of induction therapy focus primarily on concerns of increased morbidity and mortality from overimmunosuppression:

1. *Increased risk of infection*. Increased risk of cytomegalovirus (CMV) (97,98) and other opportunistic infections have been described with the use of induction therapy. The limitations of these studies include the retrospective design, the lack of control for anti-CMV prophylaxis, and the inclusion of both monoclonal and polyclonal induction regimens. The effect of this increased infection rate on mortality has not been clearly examined.
2. *Increased risk of PTLD with induction therapy*. OKT3 is associated with a significant increase in the incidence of PTLD (84). However, as yet no increase in PTLD has been found with the use of polyclonal induction therapy (99).
3. *Risk of OKT3 for treatment of steroid-resistant rejection in patients previously treated with OKT3 (either as induction or as rejection treatment)*. The incidence of sensitization to OKT3 reportedly occurs in 14% to 41% of patients previously treated with OKT3 and may be associated with acute rejection and graft loss (100). Hence, repeat administration of OKT3 is not recommended unless OKT3-specific antibodies have been tested for.

At this time there is a lack of definitive data supporting the routine use of perioperative antilymphocyte antibody therapy in *all* patients undergoing cardiac transplantation. There is some evidence, however, that certain subgroups of patients may benefit. The use of newer induction agents such as basiliximab and daclizumab is likely to be associated with a reduction of some concerns regarding induction therapy and may result in significantly improved short and long term outcomes. However, further data are awaited before high grade recommendations can be made on their use. The adverse effects of induction therapy should be minimized with judicious use of these agents. The use of antiviral prophylaxis may be beneficial in this setting.

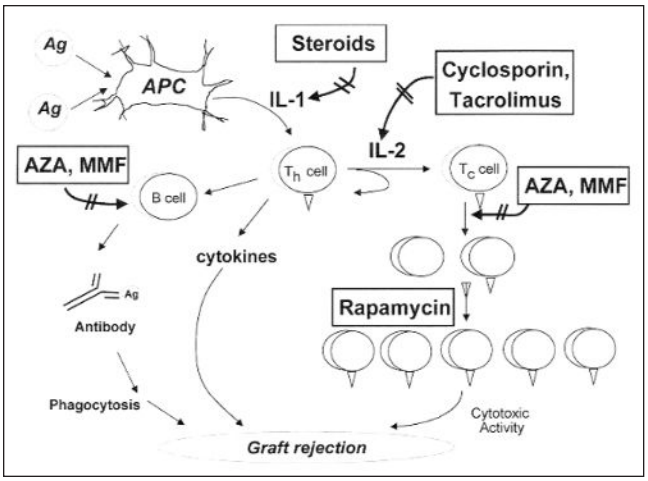

Figure 1) *Sites of action of antirejection drugs. Ag Antigen; APC Antigen-presenting cell; AZA Azathioprine; IL Interleukin; MMF Mycophenolate mofetil; Tc T cell; Th T helper cell*

5. Recommendation: Induction therapy

1. Induction therapy with polyclonal antibodies may be beneficial in subgroups of patients, such as those with significant renal or hepatic dysfunction, patients at high risk for rejection and diabetics with refractory hyperglycemia (**grade B, level 2**).

Maintenance therapy

The goal of maintenance immunosuppressive therapy is to provide freedom from rejection and graft dysfunction while minimizing toxicity from the agents used. Combinations of immunosuppressive agents can been used in an individualized approach to try to achieve this goal. Calcineurin inhibitors, purine antimetabolites and steroids are the most commonly used agents. Figure 1 illustrates the site of action within the immune response cascade of commonly used antirejection drugs.

Calcineurin inhibitors: This class of agents includes cyclosporin A (Neoral, Sandimmune, CyA) and tacrolimus (Prograf, FK506). The introduction of cyclosporin immunosuppression in 1980 was arguably the most important single advancement in the management of patients after organ transplantation. By improving both short and long term survival, primarily by reducing rejection and infection rates, the use of cyclosporin A was instrumental in making cardiac transplantation a feasible and accepted treatment for end-stage heart disease.

Cyclosporin A exerts its immunosuppressive effect by binding to a cytosolic protein, forming a complex that binds to calcineurin and subsequently blocks IL-2 transcription and synthesis. In this way cyclosporin A diminishes a key stimulator to lymphocyte activation and proliferation. Cyclosporin A also blocks upregulation of adhesion molecules and other factors, therefore reducing downstream inflammatory events.

TABLE 2
Drug interactions with calcineurin inhibitors

Drug	CNI level	Renal and additional effects
Allopurinol	↑↑	Increases serum creatinine levels; increases CNI toxicity
Amlodipine	↑↑	Increases gingival overgrowth
Amphotericin B	↑	Nephrotoxic
Cimetidine	↑	Nephrotoxicic; may delay absorption of cyclosporin A
Diclofenac		Nephrotoxic; increases AUC of diclofenac
Diltiazem	↑↑	Decreases CNI-induced nephrotoxicity (but not chronic nephrotoxicity); prevents delayed graft function and rejection; reduces ATN; increases gingival enlargement with cyclosporin A
Erythromycin	↑↑	Nephrotoxic (secondary to increased CNI levels); increases hepatotoxicity
Fluconazole/ itraconazole	↑↑	Nephrotoxic; inhibits cytochrome P450 metabolism
Gentamicin		Nephrotoxic
Ketoconazole	↑↑	Nephrotoxic (secondary to increased CNI levels); hepatotoxic; toxic to central nervous system; causes glucose intolerance; worsens gingival hyperplasia; has gastrointestinal adverse effects; causes grand mal seizures
Methotrexate	↑	Methotrexate and cyclosporin A can inhibit each other's elimination. This may result in increased levels of both
Metoclopramide	↑↑	May increase the absorption of CNI
Naproxen		Nephrotoxic; reduces glomerular filtration rate
Phenobarbital	↓↓	May induce cytochrome P450 3A4 metabolism of CNI
Phenytoin	↓↓	May induce cytochrome P450 3A4 metabolism of CNI; increases gingival hyperplasia
Ranitidine	↑	Nephrotoxic; hepatotoxic; causes thrombocytopenia
Trimethoprim/ sulphamethoxazole	↑↑	Nephrotoxic; reports of increased cyclosporin level with HPLC assay
Ticlopidine	↓↓	Alters metabolism of CNI
Vancomycin	↑	Nephrotoxic
Verapamil	↑↑	Protective renal effect; decreases nephrotoxicity; gingival hyperplasia

↑ increases; ↑↑ markedly increases; ↓ decreases; ↓↓ markedly decreases; ATN acute tubular necrosis; AUC, area under the curve; CNI calcineurin inhibitor (cyclosporin A or tacrolimus); HPLC high performance liquid chromatography

Cyclosporin A use may be associated with significant adverse effects. Cyclosporin A nephrotoxicity can be acute or chronic, and can lead to permanent renal dysfunction including renal failure. Acute renal toxicity is usually dose related, and is exacerbated by hypovolemia. Reduction of cyclosporin A dose or temporary discontinuation of cyclosporin A may be required to improve renal function, and adequate hydration must be maintained. The mechanism of renal dysfunction is thought to be related to intrarenal afferent arteriolar vasoconstriction through calcineurin inhibition, inhibition of renal prostaglandins or increased thromboxane production. Cyclosporin A nephrotoxicity can be exacerbated by concomitant use of other nephrotoxic medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs) or aminoglycosides. Agents that increase cyclosporin A concentrations can also potentiate cyclosporin-induced renal dysfunction.

Hypertension is commonly associated with cyclosporin A, occurring in up to 68% of patients (3). The mechanism may be related to its renal effects, as well as to its inhibitory effects on nitric oxide synthase. The concomitant use of corticosteroids is probably contributory. Treatment of hypertension includes maintaining the lowest feasible dose of cyclosporin A and steroids, but most patients will also require pharmacotherapy with standard antihypertensive agents (see below).

Hyperlipidemia, with increases in both serum cholesterol and triglyceride levels, is seen in about 40% of patients at one and five years after transplantation (3). Given that TCAD is a major contributor to mortality and morbidity after cardiac transplant, optimization of lipid status is of key importance (see below).

Neurotoxicity is also frequently seen with the use of cyclosporin A. This can range from tremors (common) and headache (particularly early after transplantation when cyclosporin A levels are highest) to seizures, paresthesias and mood disorders. Hypomagnesemia, also common with cyclosporin A use, may contribute to these neurological side effects. Reduction of cyclosporin A doses and magnesium replacement are often beneficial. Besides hypomagnesemia, other metabolic abnormalities such as hyperkalemia, hyperglycemia and hyperuricemia may occur. Mucocutaneous side effects such as gingival hyperplasia and hypertrichosis can be unpleasant and problematic for patients, and are most readily treated by discontinuation of cyclosporin A or by switching to tacrolimus. Hepatotoxicity typically manifest by increases in liver enzymes and usually resolves with reduction in cyclosporin A dose. There is concern that patients with preexisting liver dysfunction are predisposed to cirrhosis if treated with cyclosporin A, though this has not been shown in cardiac transplant recipients. Reduced testosterone levels have been associated with cyclosporin A use. While malignancies, including lymphoproliferative disorders, skin cancers and solid organ tumours, are more common in patients receiving cyclosporin A than in the general population, this appears to be a function of immunosuppression rather than specific to cyclosporin A use.

Cyclosporin A is metabolized in the liver and small bowel by the cytochrome P450 system and is excreted primarily in the bile. Its metabolites are less immunosuppressive than the parent compound. Drug interactions are common due to modulation of cytochrome P450 activity. Table 2 lists common drug interactions with calcineurin inhibitors. Absorption of cyclosporin A was incomplete and unpredictable with the Sandimmune preparation, influenced by food, amount of bile flow and gastric or intestinal dysmotility. The Neoral formulation provided more rapid, complete and predictable absorption, allowing improved bioavailability of cyclosporin A and reduced intrapatient variability of drug levels. This formulation has been shown to be at least as effective as Sandimmune in preventing rejection (101,102). Neoral administration also

results in blood levels comparable with those achieved with intravenous therapy within 48 h, reducing or eliminating the need for intravenous cyclosporin in most patients, except in those unable to take oral preparations.

Monitoring of serum cyclosporin A levels is essential to ensure adequate antirejection activity while minimizing adverse effects. Target cyclosporin A levels depend on the time since transplantation and are presented below. Actual cyclosporin A levels in each patient should be individualized depending on occurrence of rejection episodes or adverse effects.

Cyclosporin trough levels

0–3 months	3–6 months	6–12 months	>12 months
300–400 ng/mL	200–300 ng/mL	150–250 ng/mL	100–150 ng/mL

It has been suggested that peak cyclosporin A concentration is most reflective of cyclosporin A toxicity, while total drug exposure (area under the curve [AUC]) best correlates with therapeutic efficacy. Because sequential blood monitoring to establish AUC is impractical, traditionally trough levels have been measured as a surrogate. The assumption that trough levels accurately or consistently correlate with drug exposure has recently been challenged. Limited sampling strategies have been proposed to more accurately assess drug exposure. These include two-point sampling at 0 and 2 h after dosing and, more recently, one-point sampling at 2 h after dosing (C2 monitoring). One-point sampling has garnered interest for its practicality of application and good correlation with AUC (103). Preliminary studies suggest that C2 monitoring may be associated with greater clinical benefit, in terms of reduced acute rejection and less renal impairment, than trough level monitoring (104).

Various cyclosporin A assays are available and it is important to know which assay your centre uses. These assays include a polyclonal radioimmunoassay, fluorescence polarization immunoassay, TDX, axysm and high performance liquid chromatography (HPLC). A clinically important difference in these methods is the tendency for fluorescence polarization immunoassay to measure less active cyclosporin A metabolites, while HPLC measures only the parent compound. Radioimmunoassay is slightly less specific, but levels tend to be similar to those measured with HPLC. Familiarity with the assay used in your centre and avoidance of comparisons of levels obtained by different assays is recommended.

Tacrolimus exerts its immunosuppressive effects in a way similar to cyclosporin A. Cytokine (IL-2) synthesis is inhibited through binding of tacrolimus to a cytosolic protein (FKBP as opposed to cyclophilin) and subsequent inhibition of calcineurin. The formation of other soluble mediators of inflammation is reduced and IL receptor expression is inhibited by tacrolimus. The use of tacrolimus-based rather than cyclosporin A-based immunosuppression has been shown to result in a similar incidence of rejection (96,105,106). Tacrolimus has also been shown to be effective in the treatment of acute rejection episodes (107-109). Which agent is to be used (cyclosporin or tacrolimus) is often decided according to the toxicity profile and the individual patient.

Tacrolimus is associated with a variety of adverse effects, many of which are dose related. Early studies suggested increased adverse effects such as nephrotoxicity with tacrolimus. Overly aggressive dosing and the use of intravenous preparations were felt to be responsible, and adverse effects have been reduced with lower dose protocols and the avoidance of intravenous use (110). Nephrotoxicity remains a concern as with cyclosporin A. Similarly, high drug levels, hypovolemia and concomitant use of other nephrotoxic drugs can exacerbate renal impairment. Hypertension may be less common with tacrolimus than with cyclosporin A; however, this has not been found in all studies (111,112). Studies have shown that hyperlipidemia is much less common with tacrolimus (105) and that in fact lipid levels fall when patients are switched from cyclosporin A-based to tacrolimus-based therapy (113). Whether this has a clinically significant impact on patient outcome – for example, reduced TCAD – is yet to be determined. Tacrolimus has been associated with increased risk of hyperglycemia and development of diabetes compared with cyclosporin A, as high as fivefold in some studies (112,114), though lower dose regimens may reduce the incidence (115). Diabetes appears to be most prominent in black patients. Hyperkalemia can occur with tacrolimus use, similar to the occurrence with cyclosporin A. Neurological side effects, including tremors, paresthesias, insomnia, psychosis and confusion, are more common with tacrolimus-based immunosuppression. Patients with moderate to severe neurotoxicity may require conversion to a cyclosporin A-based regimen (109,112,114). Gastrointestinal adverse effects, including nausea, diarrhea and anorexia, may occur. Accelerated bone loss has been described with tacrolimus and is likely exacerbated with the use of corticosteroids (116).

Tacrolimus has good intestinal absorption, and intravenous use is rarely required and not recommended. The bioavailablity is variable, and careful drug monitoring is required. Tacrolimus undergoes extensive hepatic metabolism, and hepatic dysfunction or cholestasis can result in markedly increased drug levels. Renal dysfunction does not affect tacrolimus levels.

As with cyclosporin A, careful drug level monitoring is important to maintain adequate efficacy and reduce drug toxicity. Tacrolimus levels can be monitored in either whole blood or plasma using enzyme-linked immunosorbent assay techniques. Whole blood tacrolimus levels have been shown to correlate well with rejection and toxicity, though plasma levels may correlate more closely with clinical events. Whole blood monitoring is less technically difficult than plasma monitoring, and as such has been the most widely used in the clinical setting. Trough level monitoring has been the standard of care, with initial whole blood trough level targets of 10 to 20 ng/mL and a target of 5 to 15 ng/mL four weeks after transplantation. Higher levels correlate with reduced rejection, but increased toxicity and target levels should be tailored to specific patient situations.

Tacrolimus trough levels

0–3 months	After 3 months
10–20 ng/mL	5–15 ng/mL

As with cyclosporin A, trough levels are not consistently predictive of drug exposure. Strategies for use of C2 and C3 peak drug levels have been assessed (117) and preliminary data suggest that C2 monitoring may be of benefit in heart trasplant recipients to lower rejection and toxicity (118).

Many commonly used medications interact with calcineurin inhibitors and may result in potentially significant

increases or decreases in drug levels. This can have important effects on the level of immunosuppression and on the presence and severity of adverse effects such as nephrotoxicity. As well, these interactions can be used to raise levels in certain patients where it is difficult to achieve targets. Table 2 lists common interactions. Grapefruit juice and St John's wort have also been shown to raise cyclosporin levels. When adding any new medications in the setting of calcineurin inhibitor use, the potential for drug interaction should be assessed and dealt with appropriately.

Purine antimetabolites: *Azathioprine* (Imuran) in combination with corticosteroids was the first immunosuppressive regimen show to have a benefit in the prevention of solid organ rejection. Azathioprine interferes with normal purine pathways, inhibiting both DNA and RNA synthesis. Both B and T lymphocyte proliferation is suppressed, and secondary antibody synthesis is reduced. Adverse effects of azathioprine include bone marrow suppression, hepatic dysfunction and gastrointestinal upset. *Marked increase in bone marrow toxicity is seen with the concurrent use of allopurinol*, due to increased azathioprine levels.

In an effort to optimize immunosuppression while limiting toxicity from individual drugs, triple therapy using cyclosporin A, azathioprine and corticosteroids had been the standard regimen for solid organ transplantation for much of the past two decades. With the introduction of new, more specific and more powerful purine antimetabolites, such as mycophenolate mofetil (MMF), azathioprine is used less often in cardiac transplant recipients. Patients who received a transplant before the introduction of MMF may be maintained on azathioprine therapy if they have been stable and rejection free.

MMF (CellCept) is a purine analogue antimetabolite that is much more potent and selective than azathioprine. It is a relatively selective inhibitor of lymphocyte proliferation, without significant effects on other proliferating tissues. Both B and T cells are inhibited, leading to reduction of both cell-mediated and humoral immunity. Initial clinical studies of MMF in cardiac transplantation were performed using this agent as a replacement for azathioprine within triple-therapy regimens (with cyclosporin and steroids) in patients with rejection (119,120). These studies showed that MMF is an effective rescue therapy in the management of cardiac transplant rejection. A large scale international trial of 650 patients in 28 centres randomized patients to MMF versus azathioprine after cardiac transplantation with cyclosporin and steroid background therapy. The use of MMF resulted in significant reduction in need for treatment for rejection and in overall mortality at one year (121). Longer term analysis has confirmed that this benefit extends to three years after transplantation, with reduced graft loss due to rejection and a 36% reduction in overall mortality (122). Given that MMF is more costly than azathioprine and that rejection is most likely to occur in the first year after transplantation, it was postulated that patients could be switched to azathioprine after the first year to save costs. Unfortunately, late conversion (average of 41 months after transplantation) from MMF to azathioprine in heart transplant recipients has been shown to result in increased allograft rejection (123).

MMF has been used with good efficacy in both cyclosporin A-based and tacrolimus-based immunosuppressive protocols. While the combination of tacrolimus and MMF may be associated with improved rejection rates over the combination of cyclosporin A and MMF in renal transplantation (124) no such data are available in cardiac transplantation. MMF may facilitate steroid withdrawal in cardiac transplant recipients initially given triple drug therapy.

The major adverse effects associated with MMF are gastrointestinal and hematological. Abdominal pain, nausea, diarrhea and gastritis are the most common gastrointestinal side effects and are usually mild. Dose reduction or increased frequency of dosing (for example, 500 mg four times daily rather than 1000 mg twice daily) is sometimes required, and only rarely does the drug have to be discontinued for these reasons. Hematological adverse effects include leukopenia, thrombocytopenia and rarely pancytopenia. These occur in roughly the same percentages as with azathioprine, though they tend to be more frequent with higher doses of MMF. However, there is no potentiation of bone marrow suppression with MMF and concomitant allopurinol. MMF-related bone marrow suppression usually occurs 30 to 180 days after initiation of therapy. These hematological effects are usually reversible and improve a week after drug discontinuation. No nephrotoxic or hepatotoxic, and no adverse effects on lipids have been observed with MMF. Studies involving various solid organ transplants have confirmed that the incidence of opportunistic infections is increased with MMF. Herpes simplex, herpes zoster and tissue-invasive CMV occur more frequently in MMF-treated patients, though the incidence of CMV viremia/syndrome may not be increased (121). Higher doses of MMF (for example, 3 g/day) significantly increased the incidence of infection compared with lower doses (for example, 2 g/day). With increased immunosuppression, there is a concern that malignancies may be increased; however, the incidence of nonmelanoma skin cancers is similar to that seen with other immunosuppressive drugs. There are conflicting data regarding PTLD, with one study reporting a greater incidence in patients receiving MMF than with azathioprine (125) and others (126) showing a reduction in PTLD in MMF-treated patients. The long term risk for malignancy with MMF has not yet been ascertained.

MMF is rapidly metabolized within the gastrointestinal tract to its active metabolite mycophenolic acid (MPA). MPA is metabolized in the liver to an inactive metabolite, which is excreted into the urine. The inactive metabolite undergoes significant enterohepatic circulation resulting in reformation and reabsorption as MPA. This results in secondary peaks at 12 and 24 h after ingestion and an elimination half-life of 16 h. MPA is highly albumen bound, but its free concentration is also pharmacologically active. The presence of food delays absorption. Renal dysfunction does not alter the pharmacokinetics of MPA. Oral and intravenous MMF have equivalent bioavailability.

The utility of therapeutic drug monitoring of MMF is inconclusive, and traditionally patients have been managed without drug levels. Several studies in the cardiac transplant population suggest that MMF monitoring may be of benefit; specifically, keeping levels within a target range has been associated with reduced acute rejection (127-129). HPLC has been considered the gold standard for measurement of MPA and separates MPA from its metabolites. Other assays have been developed but are beyond the scope of this discussion. Whether it is trough levels or other estimates of AUC that are beneficial for monitoring MMF therapy has not yet been determined.

Recommended ranges for MPA levels by HPLC

AUC: 30–60 mg/h/L
Trough concentration: 1.6–4.2 mg/L

It is important to note that the concomitant use of cyclosporin A is associated with a decrease in MPA levels, whereas tacrolimus does not change MPA levels. However, the concomitant use of tacrolimus and MMF frequently results in potent immunosuppression and may require a dose reduction in MMF. In pediatric patients MPA levels may vary by age, body surface area and time after transplantation.

Corticosteroids: Steroids produce immunosuppression by many mechanisms and result in a powerful and generalized anti-inflammatory response. Its primary effects are on T lymphocytes; blocking proliferation through various means, and reducing monocyte-lymphocyte cooperation and monocyte migration. Release of cytokines is reduced, and IL-2 production is directly and indirectly inhibited. Steroids also have an effect on B-lymphocytes and reducing antibody production. Steroids have traditionally had a key role in the prevention of allograft rejection. The introduction of calcineurin inhibitors resulted in a marked reduction in the doses of steroids required early after transplantation. However, steroids are still almost universally used after transplantation, both as maintenance therapy and as treatment for acute rejection episodes. Unfortunately, long term steroid use is associated with significant morbidity, and strategies to further reduce or avoid steroids have garnered support.

Steroids for maintenance immunosuppression are given orally, usually as prednisone. This preparation is metabolized in the liver to prednisolone. Plasma albumin levels affect bioavailability, with hypoalbuminemia resulting in increased bioavailablity. Steroids are inactivated by the liver; therefore, reduced hepatic function increases half-life, and drugs that induce hepatic enzymes shorten the half-life. Steroid activity and toxicity are not influenced by renal dysfunction. Steroids are usually given as a single morning dose to coincide with the normal cortisol peak. This results in less suppression of the hypothalamic-pituitary-adrenal axis than does divided dosing, without reducing immunosuppressive efficacy. Other side effects of steroids may be reduced with double-dose alternate-day administration, again without detectable loss of anti-inflammatory activity (130) but with controversial results in terms of increasing risk of rejection (131,132). The use of alternate-day steroid therapy may be beneficial in children, because the benefits on growth and other potential side effects outweigh the potential disadvantages. In adults, single morning steroid dosing is the common practice. Note that stress steroid dosing is required in transplant patients receiving regular steroid doses.

Steroid dosing regimens

Intraoperative	Methylprednisolone 500 mg intravenously
Post operative	Methylprednisolone 125 mg every 8 h ×3 doses, then prednisone 0.5 mg/kg/day orally
Maintenance	Prednisone tapered to 0.1 mg/kg/day by three to six months; subsequent steroid withdrawal as tolerated

Adverse effects of steroids are myriad and have been well described. Wound healing is compromised and adds to the risk of infection. Bone disease, including avascular necrosis and osteoporosis, can result in serious long term morbidity. Hyperglycemia and frank diabetes may occur with steroid use, but are usually related to the early higher doses, and only 5% to 10% of patients require specific treatment. Patients with pre-existing diabetes, however, may find that blood sugar control is more difficult, requiring increased therapy. Cataracts may occur in up to 10% of patients receiving high dose steroids but are usually not limiting, with 1% to 2% of patients requiring cataract surgery. Increased appetite is common with steroid use and may lead to weight gain and obesity. This may be partially due to increased caloric and carbohydrate intake, as well as by steroid-induced hyperglycemia. Hypertriglyceridemia and hypercholesterolemia are associated with steroid use. Steroids may exacerbate the hyperlipidemia associated with the use of cyclosporin A. Steroids are likely contributory to the hypertension that is so common after transplantation. Mood disorders, including euphoria, sleep disturbance and rarely psychosis, have been associated with (usually high dose) steroid use. Cushingoid features (including moon face, hirsutism, acne and truncal obesity) are common but variable in degree. Myopathy is usually seen with higher doses of steroids. Whether peptic ulceration is truly caused by steroids is somewhat controversial, but because the risk of peptic ulcer is increased after transplantation, prophylactic agents are commonly given. Skin atrophy and capillary fragility due to loss of collagen are common and can lead to loss of skin integrity from minor trauma. Growth retardation is a serious concern with the use of steroids in children.

As with all immunosuppressive agents, steroids contribute to an increased risk of infection and malignancy (particularly nonmelanoma skin cancers).

Steroid withdrawal, historically associated with increased rejection risk, has received renewed interest since the introduction of newer immunosuppressive agents. Steroid withdrawal is commonly successful in liver transplantation but is associated with increased risk of rejection episodes in renal transplants (133), though it is not clear that this translates into worsened graft function or long term outcomes. In cardiac transplantation, concerns have risen over potential increased risk of acute or chronic rejection when steroids are withdrawn. Data regarding steroid withdrawal in adult cardiac transplant recipients are limited, usually consisting of uncontrolled trials in small numbers of patients. Low incidences of rejection and transplant arteriopathy were found in 32 patients who were successfully weaned off steroids onto tacrolimus monotherapy (134). Patients were followed up for only a mean of two years, too short a time for a clear assessment of the impact on TCAD. Patients at high risk of failed steroid withdrawal are those with more than three prior episodes of acute rejection (ISHLT grade 2 or higher), a prior episode of steroid-resistant rejection or rejection associated with hemodynamic compromise, and patients who could not tolerate cyclosporin A or azathioprine. Patients successfully weaned off steroids had fewer treated infections, improved mortality and no increase in either late rejection or clinically significant TCAD (135).

Rapamycin: Rapamycin (Rapamune, sirolimus) is a macrolide with mild antifungal activity that is structurally related to tacrolimus. Rapamycin selectively inhibits a later stage in the immune cascade, blocking the downstream effects of IL-2 receptor and CD28 signalling, antagonizing cytokine and growth factor action. It is a powerful immunosuppressant that has been shown to be potently synergistic with cyclosporin A

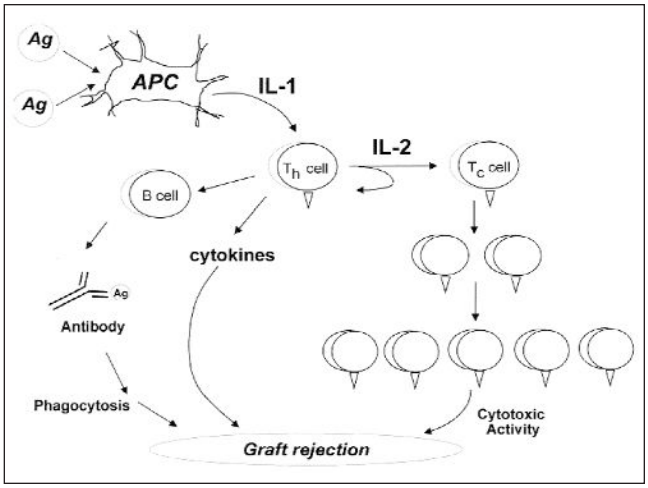

Figure 2) *Simplified scheme of immune mechanisms of graft rejection. Ag Antigen; APC Antigen-presenting cell; IL Interleukin; Tc T cell; Th T helper cell*

and MMF, but not with tacrolimus. Side effects include thrombocytopenia and hypercholesterolemia. In animal models, rapamycin has been shown to be effective in the prevention and treatment of cardiac allograft rejection and in the prevention of allograft CAD. Absorption of oral rapamycin is unpredictable and varies significantly among patients. A rapamycin derivative, SDZ RAD, has improved pharmacokinetic properties and may resolve the problems with rapamycin absorption.

The successful use of rapamycin as rescue therapy for refractory acute cardiac rejection has been documented (136,137). In renal transplant recipients, rapamycin has been effective in reducing rejection and allowing steroid withdrawal when used in combination with cyclosporin A (138,139). Trials of rapamycin and its derivative SZD RAD are underway in cardiac transplant recipients. The recommended target dose for rapamycin is 5 to 15 ng/mL. SDZ RAD (Certican) has now been shown to significantly decrease rejection and TCAD (140).

6. Recommendations: Maintenance therapy

1. Maintenance immunosuppressive therapy after cardiac transplant should be individualized and initially consist of the following:
   a) a calcineurin inhibitor (**consensus**) chosen on the basis of centre specific experience (**grade C, level 4**) and individualized needs (**consensus**);
   b) MMF (**grade A, level 1**);
   c) and corticosteroids (**grade B, level 2**).
2. MMF should be continued as part of maintenance antirejection therapy, because changing back to azathioprine is associated with increased acute rejection (**grade B, level 2**).
3. Steroids are beneficial in the early post-transplant period, but efforts should be made to use low doses to minimize adverse effects. Patients at low risk for rejection should have steroid withdrawal attempted, with appropriate vigilance for rejection and allograft CAD (**grade C, level 3**).
4. Rapamycin may be used for rescue therapy in refractory acute rejection, but primary use for maintenance therapy cannot be recommended pending clinical trial results (**grade C, level 5**).
5. Appropriate and ongoing protocols to monitor for side effects of antirejection medications should be in place (**consensus**).
6. Cyclosporin A levels may be monitored using trough levels, but C2 monitoring may provide a better assessment of drug exposure, resulting in the maintenance of therapeutic drug levels with reduced toxicity. The optimum target levels for C2 monitoring should be determined and evaluated (**grade C, level 3**). Monitoring of tacrolimus levels is strongly recommended (**consensus**).
7. Monitoring of MPA levels may be beneficial in cardiac transplant recipients for the optimal dosing of MMF and reduction of rejection (**grade C, level 3**).

POST-TRANSPLANT COMPLICATIONS

Rejection

Introduction and definition: Rejection is the process of destruction of genetically foreign organs or tissues by the host's immune system. It is a natural response, the severity and timing of which depend on the degree of genetic dissimilarity between donor and recipient, the type of organ or tissue engrafted and its complement of antigen presenting cells, and the presence of presensitization of the recipient. In clinical transplantation, rejection is a major cause of graft loss and dysfunction. This response can be modified or suppressed by various treatments, as discussed below.

Incidence and effect on graft survival: Although acute graft rejection remains an important potential cause of mortality and morbidity after transplantation, its incidence and impact on graft survival has decreased over the years as immunosuppressive regimens have improved. While the majority of cardiac transplant recipients will have at least one episode of rejection in the first year after transplantation, these are usually asymptomatic rejections identified on routine surveillance endomyocardial biopsy (EMBx), which are easily treated and do not result in significant morbidity or mortality. Rejection accounts for about 7% of deaths occurring in the first 30 days after transplantation, 18% of deaths between 31 days and one year, 10% of deaths from one to three years and only about 5% of deaths after three years (3).

Chronic rejection is essentially due to chronic vascular injury to the graft. It is typified by circumferential thickening of the vascular intima, resulting in concentric arterial narrowing, and eventually results in graft ischemia. In the cardiac transplant patient, this process is termed allograft or transplant coronary artery disease (TCAD), and is discussed in detail below (3).

Mechanisms of rejection: Graft rejection generally consists of both a nonspecific and an antigen-specific immune response. The antigen-specific immune response is the primary factor in most graft rejection. The events leading to organ rejection can be initiated in two ways. The presence of presensitization (that is, preformed antibodies) of the recipient to the donor graft leads to hyperacute rejection. If no presensitization is present,

rejection begins with activation of host T helper cells, primarily CD4-positive (CD4+) T lymphocytes, by an antigen-presenting cell with surface class II major histocompatibility complex and costimulatory activity. Once the CD4+ T lymphocyte is activated, it secretes a variety of lymphokines, which in turn attract and activate macrophages and stimulate further T cell proliferation. Cytokines are produced by CD4+ T cells (for example, tumour necrosis factor) and macrophages (for example, IL-1) and, along with the direct cytotoxic effects of other T cells, result in tissue destruction. T cell-produced antibody can initiate B cell activation with resultant complement fixation and immune complex-mediated toxicity. Thus, while T helper cells are the initial players in graft rejection, there is a downline contribution to the process from other immune system cells (Figure 2).

Identification of the cardiac transplant recipient at greatest risk for rejection has been controversial. Most, but not all, studies suggested that female recipient or donor sex and younger recipient age have been associated with increased risk of rejection. Longer allograft ischemic time and previous rejection may also increase rejection risk (131-143). The major post-transplantation risk factor for the development of rejection is the type and intensity of the immunosuppressive regimen used (see above).

Hyperacute rejection: Potential graft recipients may develop antibodies after exposure to major histocompatibility complex antigens through a prior transplant, pregnancy or blood transfusions, which are reflected in an elevated PRA titre. These preformed antibodies may lead to an immediate and profound immune response leading to immediate graft failure upon revascularization. This is termed hyperacute rejection, and the mechanism of immediate tissue destruction is presumed to be that of local fixation of complement by antibody bound to the graft. This is primarily a vascular process, and histology reveals antibody and complement deposition and polymorphonuclear leukocyte infiltration in these cases. Hyperacute rejection can be pre-empted by adequate antibody crossmatch and blood group matching (see above) but cannot be easily reversed once initiated. Hyperacute rejection is a rare cause of graft loss (less than 1% of all organ grafts).

Acute rejection: Activation of the immune system, initiated by antigen-presenting cell contact with T helper lymphocytes, can result in graft dysfunction and loss. Typically this process occurs more than five days after transplantation and is most frequently seen in the first three months. However, acute rejection can occur at any time, often in response to a reduction or discontinuation of maintenance immunosuppressive therapy. Episodes of acute rejection are common in current clinical cardiac transplantation (about 50% will have one or more episodes over the life of the graft) but are often mild and usually respond well to therapy. Most episodes of acute rejection are asymptomatic and diagnosed on surveillance EMBx, though clinical signs and symptoms of graft dysfunction may occur as rejection progresses.

Acute graft dysfunction may occur in the absence of typical histological evidence of cellular rejection. Microvascular immune-mediated injury may be present in the absence of cellular infiltrate and necrosis and is therefore more challenging to diagnose. Stains for immunoglobulin G and complement may identify the presence of microvascular injury. This process may be referred to as *humoral* or *vascular rejection*.

Diagnosis: Typically, clinical signs and symptoms of rejection do not occur until rejection is advanced. Before the introduction of cyclosporin in 1980, electrocardiographic monitoring (QRS voltage assessment and comparisons) was helpful in predicting the presence of cardiac allograft rejection. However, electrocardiographic indicators of rejection were less sensitive when cyclosporin was used and therefore currently early diagnosis of cardiac rejection relies on the histological diagnosis through EMBx. While the majority of rejection episodes are asymptomatic, hemodynamically compromising rejection may occur. Hemodynamically compromising rejection is defined as a decrease in ejection fraction of more than 10% or the presence of clinical signs of ventricular dysfunction (elevated jugular venous pressure, pulmonary rales, third heart sound, etc), and is associated with a high incidence of graft failure and mortality.

Practical tips for clinicians: Presentation of rejection

Asymptomatic: (majority of episodes)

Symptomatic:
- Fever
- Malaise
- Reduced exercise tolerance
- Hypotension
- Congestive symptoms
- Clinical findings of CHF

EMBx: EMBx has been the gold standard for diagnosis of cardiac allograft rejection. Percutaneous EMBx became feasible with the development of specialized transvascular bioptomes, the first of which required a femoral approach, but subsequent bioptomes have made the transjugular approach the most widely used. Both left and right ventricular EMBx can be performed, though the vast majority of EMBx are from the right ventricle. Description of the technique for percutaneous EMBx is beyond the scope of this document but is well described elsewhere (144). Of note, EMBx are associated with a very low morbidity and mortality, lower than those accompanying renal and liver biopsies, when performed by an experienced operator. Traditionally, EMBx have been performed under fluoroscopic guidance, usually in the cardiac catheterization laboratory. More recently, echocardiographic guidance has been used and may have advantages such as reduced sampling error, ability to assess ventricular and valvular function during the procedure, reduced complication rate and reduced cost (145,146).

In most centres, EMBx is used for routine rejection surveillance. EMBx is first performed at days 10 to 14 after transplantation if induction therapy is used (147) and may be performed earlier in the absence of induction therapy. Typically, weekly biopsies are performed for four weeks, and the time interval between biopsies is then increased gradually. In the absence of clinical evidence of graft dysfunction, major changes in immunosuppressive regimen or continued histological evidence of rejection, routine EMBx are less frequently required after the first year following transplantation. ISHLT Registry data, however, suggest that acute rejection does remain an issue up to three to five years after transplantation (3), so many centres continue to perform at least annual routine surveillance EMBx until five years after transplantation. There are no clinical trials comparing management of cardiac transplant recipients with and without EMBx guidance, nor are there trials looking at the optimum timing and frequency of EMBx.

TABLE 3
International Society of Heart and Lung Transplantation grading system for endomyocardial biopsies

Grade	Findings
0	No rejection
1A	Focal (perivascular or interstitial) infiltrate
1B	Diffuse but sparse infiltrate
2	One focus only of aggressive infiltrate or focal myocyte necrosis
3A	Multifocal aggressive infiltrates with myocyte necrosis
3B	Diffuse aggressive infiltrates with myocyte necrosis
4	Diffuse, aggressive polymorphous appearance with or without edema, hemorrhage or vasculitis

ISHLT standardized grading of cardiac transplant rejection: Various schemes for the histological grading of cardiac allograft rejection have been proposed, but the most widely used, accepted and well-developed grading system is that of the ISHLT. This system was developed and introduced to allow standardization in the assessment of severity of rejection on EMBx and to serve as a guide to treatment (148). EMBx samples should be assessed for histological evidence of rejection and should be graded according to the ISHLT grading system (Table 3).

Noninvasive methods of rejection screening: Despite the extensive experience with using EMBx for the early diagnosis of cardiac allograft rejection, there continue to be problems with this 'gold standard'. These include concerns about nonuniform distribution of myocyte lesions with the potential for sampling error, difficulty with interpretation of histological findings and the need for repeated invasive procedures to obtain tissue for assessment (with the risk of complications). For these reasons, new diagnostic methods are being evaluated in an effort to detect early rejection. LV function should be assessed by either echocardiography or angiography in patients with suspected or biopsy-proven rejection to rule out hemodynamically compromising rejection. Many noninvasive diagnostic approaches have been studied including the use of electrocardiographic indicators, echocardiographic indexes, immunological markers, biochemical markers, radionuclide scanning and magnetic resonance imaging/dynamic computed tomography (CT). The ideal test would be sensitive, specific, reproducible, easily available and cost effective. The goal would be to use the noninvasive test to screen for early rejection and therefore guide the use of the invasive EMBx. Noninvasive methods under consideration and study have been reviewed in detail (149-157). As of this writing, there is no noninvasive test that is felt to have sufficient qualities to replace the current use of surveillance EMBx.

7. Recommendations: EMBx

1. Right ventricular EMBx, performed under fluoroscopic or echocardiographic guidance, remains the gold standard for surveillance and detection of early cardiac allograft rejection (**consensus**).
2. The ISHLT standardized grading system for histological assessment of EMBx should be used for diagnosis of severity and to guide therapy of cardiac allograft rejection. Histological assessment should be performed by a pathologist with expertise in the evaluation of EMBx for rejection (**consensus**).

Treatment: Despite strategies to prevent cardiac allograft rejection, the majority of patients will experience at least one episode of rejection, usually within the first year after transplantation. The majority of these episodes will be asymptomatic episodes of cellular rejection diagnosed on routine surveillance EMBx. The goal of treatment for allograft rejection is to use the lowest amount of immunosuppression possible to effectively manage the episode, while minimizing potential side effects.

The treatment of rejection episodes depends on the grade of rejection present, the presence or absence of symptoms of graft dysfunction and the timing of the episode after transplantation. In general, symptomatic rejection and episodes occurring within 30 days of the transplant will require higher intensity immunosuppression than asymptomatic rejection and than episodes occurring later after transplantation.

Even in the absence of symptoms of allograft dysfunction, cardiac imaging (for example, echocardiography or multiple gated acquisition) is useful in monitoring graft function in the setting of biopsy-proven rejection.

Treatment of cellular rejection: Asymptomatic *mild rejection (ISHLT 1A or 1B)*, in the absence of LV dysfunction, occurring after the first 30 days after transplantation is usually not treated specifically, other than to ensure compliance with medications (including ruling out the use of other drugs that may influence immunosuppressive drug levels or activity). Repeat EMBx should be scheduled sooner to evaluate the progression of severity of rejection. Oral steroid, MMF or cyclosporin doses may be increased, especially within two months of transplantation (158) according to the preferences and experience of each site. If steroids are being tapered, then tapering should be suspended, at least temporarily. Published data suggest that up to a third of grade 1A or 1B rejections may progress to moderate rejection on follow-up biopsy (159,160). These data were obtained before the routine use of MMF and may not be representative of the natural history with current immunosuppressive regimens.

The importance of *focal moderate rejection (ISHLT 2)* has been debated, and at one point this was temporarily removed from the ISHLT grading system. Focal moderate rejection is almost always asymptomatic, and only 11% to 15% progress to higher grade rejection (161). It has been suggested that ISHLT 2 rejection may in many cases result from Quilty lesions rather than being true rejection (162). The significance of Quilty lesions is unclear. There is no apparent association with graft vascular disease, reduced survival or development of rejection on subsequent biopsies. The potential importance of distinguishing this grade from mild rejection has been suggested by data indicating that in patients less than six months after transplantation almost 90% of ISHLT 2 biopsies progressed to ISHLT 3A (moderate rejection), whereas only 4% progressed to high levels in patients more than six months after transplantation. In general, ISHLT 2 rejection is treated similarly to mild rejection, with repeat biopsy, with or without increased steroid or cyclosporin doses.

Approximately 90% of *moderate rejection (ISHLT 3A or 3B)* episodes are associated with normal hemodynamics; however, this grade of rejection probably does require therapy, even when asymptomatic. High dose intravenous steroids have traditionally been used to treat moderate rejection, particularly that occurring early after transplantation. There is evidence that oral pulsed steroids can be used to successfully treat

asymptomatic moderate rejection when it occurs more than 30 days after transplantation. In addition to similar efficacy as intravenous steroids, the oral protocol has similar infectious complications but is more convenient and cost effective (163,164). Moderate rejection episodes occurring in the first 30 days after transplantation should be treated more aggressively, usually with intravenous steroids. Moderate rejection associated with evidence of hemodynamic compromise should be treated with a combination of intravenous steroids and cytolytic therapy (OKT3 or antithymocyte globulin). Follow-up biopsies should be performed seven to 14 days after treatment to monitor rejection status in all cases.

Severe rejection (ISLHT 4) is usually symptomatic and is treated as for symptomatic or hemodynamically compromising moderate rejection, with steroids and cytolytic therapy. Severe rejection carries a high incidence of graft failure and mortality.

Persistent rejection is where a biopsy grade of 3A or greater is present on two or more consecutive biopsies and requires treatment and augmentation of immunosuppressive therapy. In the case of steroid-resistant rejection (two consecutive episodes of rejection treated with steroids, not resulting in resolution of rejection) cytolytic therapy should be administered. In the case where cytolytic therapy has been unsuccessful, other pharmaceutical options include conversion from cyclosporin A to tacrolimus, conversion of azathioprine to MMF (if not already done) and the use of rapamycin, cyclophosphamide or methotrexate. Nonpharmaceutical options include total lymphoid irradiation, plasmapheresis or photopheresis (a leukapheresis-based therapy that uses 8-methoxypsoralen and ultraviolet A irradiation) (165).

Treatment of humoral or vascular rejection: Acute graft dysfunction may occur in the absence of typical histological evidence of *cellular rejection*. Microvascular immune-mediated injury may be present in the absence of a cellular infiltrate. This process is referred to as *humoral* or *vascular rejection*. This type of rejection is more severe, often resistant to standard forms of antirejection therapy, and is associated with a worse prognosis. Treatment protocols using high dose steroids, cyclophosphamide and plasmapheresis have been associated with improved survival and graft function (166). Small studies have used high dose human immunoglobulin as an effective treatment for humoral rejection in renal and cardiac transplant recipients (167).

8. Recommendations: Treatment of rejection

1. Mild and focal moderate rejection may be treated with an increase in steroid or calcineurin inhibitor dose, but usually does not require specific therapy (**grade B, level 2**).
2. Moderate and severe rejection should be treated with intensified immunosuppression. Asymptomatic moderate rejection occurring more than 30 days after transplantation can be managed with oral pulsed steroids. Early moderate rejection usually requires intravenous steroids, while severe or symptomatic moderate rejection at any time after transplantation should be managed with a combination of cytolytic therapy and intravenous steroids (**grade B, level 2**).
3. After the identification of rejection on EMBx, follow-up biopsy should be performed in seven to 14 days to assess progression of rejection and to evaluate efficacy of therapy (**grade B, level 2**).
4. Vascular (humoral) rejection should be treated aggressively. A combination of intravenous steroids, cyclophosphamide and plasmapheresis may be efficacious (**grade C, level 4**).
5. Persistent rejection despite treatment with steroids should be treated with
   a) conversion to tacrolimus (if previously on cyclosporin A)
   b) conversion to MMF (if previously on azathioprine)
   c) cytolytic agents
   d) addition of rapamycin, cyclophosphamide or methotrexate
   e) use of photopheresis (**grade C, level 3**).
6. Persistent rejection despite treatment with steroids and cytolytic agents may benefit from the use of photopheresis (**grade C, level 3**).

Infections

Background and rationale: Infections are an important cause of morbidity and mortality after heart transplantation. Aside from the usual community infections, heart transplant patients are particularly prone to infections as a result of immunosuppressive therapy. These are most likely to occur in the weeks immediately after surgery and after augmentation of immunosuppression for rejection (168).

An important number of infections are predictable based on published experience in transplantation; therefore, these can be prevented to a degree by standard protocols. However, others cannot be anticipated and are treated once diagnosed. The diagnosis and management of established infections should be in conjunction with infectious disease specialists and other specialists depending on the clinical syndrome.

Approach to infections: The timing of infections relative to the date of transplant can help predict the type of infection present. Post-transplant infections are generally classified as occurring in 1) the first month (early perioperative period), 2) the first to the sixth month and 3) beyond the sixth month (the late post-transplant period) (169). Although somewhat arbitrary, this classification nonetheless captures most of the relevant reasons for infections to develop and therefore can help guide diagnostic and therapeutic strategies.

In the first month after transplant, most infections are due to surgical complications and are therefore similar to those observed in the general cardiac surgical population. These include surgical site infections, infections associated with indwelling catheters, ventilator-associated pneumonias and urinary tract infections. Infections may be acquired during the perioperative period. To prevent surgical site infections cefazolin 1 g intravenously is given on call to the operating room. In settings with a high prevalence of methicillin-resistant *Staphylococcus aureus*, this is usually substituted with vancomycin. Less commonly, an unrecognized infection in the donor can be transmitted to the recipient (170). Of particular concern is bacteremia or fungemia in the donor, which may among other sites present as infection at the aortic suture line. Because of this risk, blood cultures of the donor should be routinely obtained. Viral infections such as herpes simplex virus can occur in the first month after transplantation, either

because the recipient was already seropositive before transplantation or rarely due to a primary herpes simplex virus infection acquired from the donor.

Between the first and the sixth month after transplantation, the common opportunistic infections that occur are CMV, herpes simplex virus, *Pneumocystis carinii*, aspergillus, nocardia and toxoplasmosis. As well, donor infections such as hepatitis or mycobacteria can surface in the immunosuppressed host.

Beyond six months after transplantation, conventional infections seen in the general population tend to occur. These include influenza and pneumococcal pneumonia. A common opportunistic viral infection seen during this period is reactivated varicella-zoster viral infection manifesting as shingles. Patients at highest risk are those who have had acute rejection requiring high dose pulse steroid or cytolytic therapy and those who have had recurrent rejections and are receiving higher doses of background immunosuppressive therapy. In these patients, opportunistic infections such as *P carinii* or viral infections (CMV or Ebstein-Barr virus [EBV]) are seen (171). Environmental exposure, such as construction in one's home, can result in exposure and infection from aspergillus.

Diagnosis: The initial approach to the patient with infection requires a thorough history and physical examination to try to localize the potential site of infection. Basic testing should include a complete blood count, hepatic and renal panels, and a chest x-ray.

In a febrile transplant patient, identification of the organism is of paramount importance. This can be achieved with site-specific cultures and biopsies of affected tissue. Blood cultures using aerobic and anaerobic media, and sputum and urine cultures should be done. For certain infections specific tests must be done; hence, it is important to specify what is suspected clinically. For instance, for *P carinii* infection, induced sputum, bronchoalveolar lavage or lung biopsy may be necessary to make the diagnosis with special tests such as methenamine silver staining or polymerase chain reaction (PCR). Therefore, coordination with microbiology and pathology departments is important to ensure that samples are tested for a broad range of organisms seen in transplant patients that are not usually sought in routine samples.

Prevention of infections: Extensive serological testing should be done in the donor and recipient including serological evaluation for latent infections that can be transmitted with the allograft: CMV, EBV, *Toxoplasma gondii* and syphilis are the most important. Donors should be evaluated for hepatitis B and C, and for human immunodeficiency virus (HIV) (172,173). Infection with hepatitis B or HIV excludes the use of the donor organ. The use of an organ from a donor who is seropositive for antibodies to hepatitis C virus is controversial because the five-year survival after transplantation does not appear to be affected but the long term consequences are unclear. Recipients should also be tested for hepatitis B and C, and for HIV. As well, they should undergo tuberculin skin testing because of the risk of reactivation of tuberculosis during immunosuppression (174).

CMV: CMV may be transmitted from the donor to the recipient. It is therefore imperative to test CMV serology in both donor and recipient. If both are negative, no prophylaxis is required. A seropositive donor or recipient requires either prophylactic therapy or ongoing assessment for CMV through serological monitoring (pre-emptive therapy). A double-blind study in cardiac transplant patients randomly assigned patients to receive ganciclovir or placebo (175). Patients were stratified into two groups: those who were seropositive for CMV before transplantation and those who were seronegative but who received hearts from seropositive donors. The treatment strategy consisted of intravenous ganciclovir (5 mg/kg twice daily) for 14 days followed by 6 mg/kg daily five days/week until day 28. In seropositive recipients, CMV disease occurred during the first 120 days after heart transplantation in 46% of patients given placebo, as compared with 9% of patients treated with ganciclovir ($P<0.001$). In the seronegative recipients with seropositive donors, CMV disease occurred frequently in both groups (placebo 29%, ganciclovir 35%, not significant). From these data, it is common practice to provide 21 to 30 days of prophylactic therapy in recipients who are seropositive before transplantation. The usual regimen is ganciclovir 5 mg/kg every 12 h for 14 days or until discharge home if this occurs before 14 days. The dose should be adjusted according to serum creatinine or white blood count, and after discharge home, ganciclovir is given orally in doses of 500 to 1000 mg twice or three times daily until about postoperative day 30.

In seronegative recipients of a CMV-seropositive donor, short courses of prophylaxis do not appear to be beneficial. Given the considerable risk of CMV disease, however, prophylactic ganciclovir is usually offered for up to 12 weeks after transplantation (176).

All patients with high risk of developing CMV disease (donor or recipient positive) should be considered for prophylaxis with antiviral agents during treatment of acute rejection with antilymphocyte agents.

Finally, in contrast to prophylactic strategies or as a complement to the prophylactic regimens outlined above, another approach is termed pre-emptive treatment. Pre-emptive treatment is based on close monitoring of asymptomatic patients with surveillance cultures, CMV antigenemia or PCR with the goal of treating patients very early or 'pre-emptively' in the infection before they become symptomatic. The benefit of this approach in the heart transplant population remains to be further clarified.

Further data are required before making recommendations regarding the use of CMV hyperimmune globulin (Cytogam) for the prevention or treatment of CMV.

Toxoplasmosis: Toxoplasmosis may also be transmitted from donor to recipient. In the case of a seropositive donor and a seronegative recipient, pyrimethamine 25 mg daily and folinic acid 15 mg daily for six months should be administered (177).

P carinii *pneumonia:* All patients should be considered at risk for *P carinii* and consideration should be given to prophylactic trimethoprim/sulphfamethoxazole 160/800 half tablet per day for at least one year. In case of sulpha allergy, dapsone or pentamidine aerosol 300 mg once a month for one year can be used.

Tuberculosis: Tuberculosis may also be reactivated after transplantation. In patients with a positive purified protein derivative test before transplantation, infectious disease consultation should be obtained and consideration given to INH 300 mg and vitamin B6 50 mg daily prophylaxis for one year.

Hepatitis B: Patients who are hepatitis B surface antigen (HbsAg) -positive at the time of transplant may have recurrence of hepatitis B infection after transplantation. These patients should be followed up closely by a hepatologist both before and after transplantation. Antiviral agents and hepatitis B virus immunoglobulin have been shown to reduce the risk of

recurrence and to convert patients from HbsAg positive to negative. Hepatitis infection can be tested by a variety of tests including measurement of hepatitis B early antigen and antibody to HbsAg (anti-HBS).

The reappearance of HbsAg suggests a relapse. Quantitative anti-HBS can help to calculate the quantity of immunoglobulin necessary to maintain adequate levels of antibody. The presence of hepatitis B or C increases the risk of cirrhosis and hepatocellular carcinoma after transplant.

Candidiasis: Oral candidiasis is common after transplantation. Mycostatin mouthwash is helpful in preventing this complication. The presence of odynophagia should alert the clinical to the possibility of underlying esophageal candidiasis.

Endocarditis: After heart transplantation, patients are at risk of developing endocarditis on the supravalvular suture line; hence, infective endocarditis prophylaxis should be given to heart transplant patients undergoing dental, gastrointestinal or genitourinary tract surgery. Antibiotic prophylaxis is not required for cardiac biopsy or other invasive procedures performed by sterile technique. Prophylaxis should be given according to standard guidelines (178).

Vaccinations: In general routine influenza vaccination is recommended after the first year following transplantation. Centre-specific guidelines dictate use of pneumovax. Hepatitis B vaccination is recommended before transplantation. Live vaccines should *not* be given.

Common infections and their management – CMV *infection:* CMV is a ubiquitous virus in the general population, in whom it causes a mild or imperceptible clinical syndrome. In the immunosuppressed patient it can have severe consequences and may be fatal. Transplant patients at highest risk for developing CMV infection are those who are seronegative for CMV and receive a seropositive donor organ.

CMV may remain in a latent state characterized by carriage of the virus without symptoms. An infection may become active at any time in immunocompromized hosts, especially during periods of acute rejection for which antilymphocytic therapy is being administered. Active infection can manifest in a variety of ways including nonspecific symptoms such as generalized discomfort, fever, myalgia and arthralgia, to more specific organ involvement including hepatitis, pneumonitis, gastroenteritis, colitis and encephalitis (176). The diagnosis of active CMV infection is suggested by high fevers and neutropenia and confirmed by positive cultures of, for example, shell vial assays, antigenemia tests or quantitative PCR from infected sites (biopsy or fluid) or from blood. Definitive diagnosis of invasive CMV disease requires histopathological evidence of CMV on tissue biopsy.

Treatment of CMV disease requires intravenous ganciclovir for two to four weeks. Follow-up CMV testing is used to determine clearance of viremia before cessation of intravenous therapy. This is performed with the dual goal of preventing clinical relapse and limiting development of resistance to ganciclovir. Anti-CMV hyperimmune globulin can be added to the treatment of severe or relapsing disease. Ganciclovir-resistant CMV may be suspected by a lack of clinical response and requires specific virological studies. The management of suspected ganciclovir-resistant CMV requires infectious disease and microbiology expertise.

Other herpes group infections that occur commonly after transplant are herpes simplex and herpes zoster (shingles). Shingles occurs commonly after transplant, and early recognition and treatment may reduce the occurrence of postherpetic neuralgia. Once postherpetic neuralgia has developed, amitriptyline, gabapentin or carbamazepine (note carbamazepine lowers cyclosporin levels) are often successful in managing symptoms.

TABLE 4
Diagnosis of fever with abnormal chest radiograph

Radiographic results	Acute onset	Subacute or chronic onset
Consolidation	Bacterial including legionella	Fungi, nocardia
	Thromboembolism	Tumour
	Hemorrhage	Tuberculosis
	Pulmonary edema	*Pneumocystis carinii*
		Virus
		Drug reaction
Peribronchovascular abnormality	Pulmonary edema	Virus
	Leukoagglutinin reaction	*P carinii*
	Bacteria	Drug reaction
	Virus – influenza	
Nodular infiltrate	Bacterial including legionella	Fungi, nocardia, tuberculosis, *P carinii* pneumonia
	Pulmonary edema	

Pneumonia/pneumonitis: Transplant patients are susceptible to common viral throat and chest infections that do no require antibiotic therapy. However, prompt diagnosis and use of specific therapy is important in transplant patients with significant pulmonary infections. Initial testing includes chest x-ray, blood and sputum cultures, and a complete blood count. It is strongly recommended that the organism responsible be determined and therefore invasive diagnostic tests may be required. The findings on x-ray may differ from the those in the immunocompetent patient; specifically, transplant patients have a depressed inflammatory response that may alter the appearance or presentation of infiltrates on an x-ray. Therefore, descriptions of typical radiographic patterns with specific infectious syndromes are less reliable in the transplant patient. Table 4 lists the differential diagnosis of pulmonary infection as seen on the chest x-ray (169).

The use of chest CT can aid in the evaluation of pneumonia by providing more descriptive information than an x-ray; however, it does not provide the specific diagnosis. The most beneficial roles of CT are that it can better delineate the extent of pulmonary involvement and can guide invasive diagnostic techniques such as needle aspiration.

Because of the broad differential diagnosis for each clinical scenario (Table 4) and the possibility of multiple infections in immunocompromized patients, a specific etiological diagnosis should be sought whenever possible. Unlike the approach to community-acquired pneumonia in immunocompetent patients that advocates empirical treatment and recognizes the low yield of diagnostic testing, a transplant patient with pneumonia should prompt early consultation with a respiratory medicine specialist. In some settings, invasive testing such as bronchoscopy (with bronchoalveolar lavage or transbronchial biopsy) is indicated before therapy is instituted. In other settings where the differential diagnosis is limited, a trial of empirical treatment may be instituted with the understanding

TABLE 5
Differential diagnosis of central nervous system infections

Clinical presentation	Causes
Acute meningitis	*Listeria monocytogenes*
Subacute/chronic meningits	*Cryptococcus neoformans*
	Tuberculosis
	Listeria monocytogenes
	Nocardia
	EBV-related PTLD
Focal neurological deficit	Aspergillus
	L monocytogenes
	Toxoplasma gondii
	Nocardia asteroides
	EBV-related PTLD
Progressive dementia	JC virus
	HSV, CMV, EBV
	Cyclosporin or FK toxicity

CMV Cytomegalovirus; EBV Ebstein-Barr virus; HSV Herpes simplex virus; JC Jacob-Creutzfelt; PTLD post-transplant lymphoproliferative disorder

that a tissue diagnosis will be sought if no clinical response is witnessed after 48 to 72 h of treatment. Early involvement of infectious disease and respirology specialists is recommended for severe infections.

Central nervous system infections: Central nervous system infections in transplant patients can differ significantly from those in immunocompetent patients. In particular, the depressed inflammatory response caused by immunosuppressive therapy can diminish signs of meningeal inflammation associated with meningitis, such that changes in the level of consciousness may be subtle. Central nervous system infection frequently presents as unexplained fever and headache. This warrants a complete neurological evaluation with CT of the head and lumbar puncture.

Central nervous system infections in transplant patients have three distinct presentations (169). The first is meningitis – acute, subacute or chronic – presenting as fever and headache evolving over days to weeks, which may be associated with an altered state of consciousness. The second is a focal brain infection that presents with seizures or focal neurological abnormalities. The third is progressive dementia, which may or may not be associated with focal abnormalities or seizures. Table 5 lists the most frequent causes of these findings.

Infectious complications in pediatric patients: EBV infection remains a significant concern in the pediatric population because of the high probability of the recipient being seronegative. Both donor and recipient EBV status should be ascertained. Prophylaxis is recommended for donor and recipient positive EBV status. Prophylaxis consists of ganciclovir and CMV hyperimmune globulin for three to four months. Surveillance should include regular assessment of EBV PCR, especially in the early post-transplant period. Primary EBV infection can be severe with multisystem involvement, especially if it occurs within the first three to six months after transplantation. Symptomatic disease requires intravenous antiviral therapy regardless of when it occurs after transplant. Conversion from a negative to a positive EBV PCR requires consideration of antiviral therapy within the first six months after transplant. Patients with a chronically positive EBV PCR should be considered for chronic antiviral therapy. Patients with a positive EBV PCR that increases by semiquantitative or quantitative measures require assessment for PTLD and consideration should be given to baseline, screening and annual radiological imaging. EBV status must be taken into consideration when managing routine immunosuppression and responding to rejection.

Most pediatric transplant recipients have not finished their routine schedule of immunizations. Titres should be extensively checked before transplantation. Efforts should be made before transplantation to immunize the child with as many vaccinations as possible and developmentally appropriate, the most important being live viral vaccines. After transplant vaccination schedules should not be resumed for six months but may then follow appropriate schedules. *Patients should never receive live viral vaccines after transplant* regardless of the fact that they are in the routine immunization schedule. Appropriate titres should be checked after vaccination to determine the response given the suppression of the immune system.

Transplant coronary artery disease

After the first year following transplantation, TCAD is the most common cause of morbidity and mortality (179). TCAD differs from classic CAD in that it is diffuse, involving all levels of the vascular tree including veins, arteries and great vessels. The vascular bed outside of the allograft is spared (180). Although classic symptoms of CAD such as angina often do not occur due to cardiac denervation, they can occur in a small percentage of patients. Often symptoms are of anginal equivalents such as shortness of breath. When cardiac symptoms do develop, they usually indicate advanced disease (181), for example, CHF, myocardial infarction and sudden death.

Pathogenesis: The pathogenesis of TCAD is likely multifactorial, with both immune and nonimmune factors implicated.

Immune-mediated factors: TCAD is associated with a donor-specific cell-mediated alloreactivity to vascular endothelium, whereas the role of humoral immunity is unclear (182). A variety of cytokines and growth factors appear to promote the development of endothelial disease and TCAD (183). Patients with two or more episodes of acute rejection within the first year after transplant requiring treatment appear to be at higher risk of TCAD (184). The number of acute rejections also appears to correlate with accelerated TCAD (185-190).

Nonimmune-mediated factors: There is evidence of an association between CMV and TCAD (191-193). CMV-infected patients appear to develop angiographically severe obstruction (70% or more) more frequently than noninfected patients, independent of the serological status before the transplant and of the presence of symptomatic infection. It is unclear whether other infectious agents, such as chlamydia (194,195), may have a role.

Hypercholesterolemia is common after heart transplantation, occurring in approximately 75% of patients (196,197). This is due to a combination of factors including obesity, medications, pretransplant hyperlipidemia, age, sex and diabetes. It is the most consistently associated metabolic risk factor for the development of TCAD (198-200). As well, lipoprotein(a) levels vary widely after heart transplantation (201-203), but when elevated (204) appear to be associated with TCAD.

Older donor age, donor male sex, donor hypertension, recipient male sex and recipient black race are also risk factors

for TCAD (204). Other nonimmune risk factors are smoking (185,188), postoperative arterial hypertension (185), elevated homocysteine levels (205,206), elevated troponin T levels (207) and cumulative prednisone dose above 15 g (189). Preexistent donor CAD documented with intravascular ultrasound (IVUS) does not necessarily accelerate the progression of TCAD within the first few years after transplantation (208). However, older donor age remains a very strong risk factor for TCAD and likely reflects the long term impact of CAD in the donor heart (3).

Screening and diagnosis: Because most patients do not experience chest pains with ischemia, TCAD is screened for routinely in most centres to detect asymptomatic TCAD.

Noninvasive tests: Noninvasive evaluation of patients for detection or surveillance of TCAD has been limited by lack of adequate sensitivity and predictive value (209), as well as by an inability to predict prognosis accurately. The imaging modality used depends largely on local expertise.

Dobutamine stress echocardiography: In a study by Akosah et al (210), dobutamine stress echocardiography (DSE) was carried out 57±5 months after transplantation. It had a sensitivity, specificity, and positive and negative predictive accuracy of 95%, 55%, 69% and 92%, respectively, when compared with coronary angiography. The VACOMED Research Group (211) documented a sensitivity of 86% and specificity of 91% of detecting important (greater than 50%) stenosis. Regional myocardial dysfunction as assessed by DSE correlates with the presence of moderate to severe intimal hyperplasia as assessed by IVUS (212). These findings suggest that DSE reliably correlates with severity of disease.

In the VACOMED study, two patients sustained an acute myocardial infarction at follow-up: both of these patients had abnormal DSE, but only one had an abnormal angiogram, suggesting that DSE may have a predictive value for identifying future ischemic events in transplant recipients. In a recent publication, a worsening of serial DSE indicated an increased risk of events (relative risk 7.26, P=0.0014) compared with no deterioration. The authors concluded that a normal DSE predicts an uneventful clinical course (213). DSE is superior to both exercise electrocardiography and coronary angiography for the prediction of subsequent cardiac events (214). The presence of inducible wall motion abnormalities seems to be predictive of angiographic TCAD, myocardial infarction or death (215). It is also appears to be a highly reproducible noninvasive test, which may be used serially in transplant recipients (216) and may reduce the need for routine angiography (212).

Myocardial perfusion imaging: Lung to heart count ratios during dipyridamole thallium testing have been assessed. Lenihan et al (217), in a study of 66 patients, found that a ratio 0.40 or greater is a sensitive predictor of coronary events, whereas patients with a ratio less than 0.40 and normal systolic LV function were at low risk for subsequent events during 21±11 months of follow-up. More studies are needed to validate these findings in the cardiac transplant population.

Postexercise versus rest dual isotope myocardial scintigraphy has been shown to have a sensitivity of 77% and specificity of 97.7% for the detection of TCAD (218). In a study by Carlsen et al (219) comparing angiography with single photon scintigraphy, the negative predictive value of normal single photon emission computed tomography was 98% for the detection of lesions suitable for revascularization.

Invasive methods: Angiography remains the most frequently used modality for the surveillance of patients after transplant. However, it has limitations related mainly to the diffuse nature of TCAD. Indeed, it tends to severely underestimate arterial narrowing because no reference point exists (220). Some centres perform a baseline angiogram (within the first month after transplantation) because statistically significant luminal narrowing may be present on serial angiograms taken during the first year after transplantation (221). There are no established guidelines concerning the role of angiography in transplant patients.

Because of the above limitations, IVUS has become a very attractive method for the identification and study of progression of TCAD over time. It gives a more accurate estimate of luminal dimensions, can identify angiographically absent atherosclerotic plaque and can characterize plaque composition. IVUS is therefore a useful adjunct to coronary angiography (222-224). IVUS may have prognostic value given the association between intimal thickness (greater than 0.3 mm) and overall survival (224). The main limitations of IVUS are cost and its restricted use to centres with IVUS facilities. The use of intracoronary Doppler can be added to IVUS to assess the physiological consequences of coronary lesions. Coronary vasodilatory or flow reserve can be determined from this technique and is usually normal early after heart transplantation (225). In the setting of acute rejection it may deteriorate (226) but rapidly recovers after treatment (227), indicating reversible microvascular injury. In the long term, a gradual decline in vasodilatory reserve is commonly observed. This seems to be directly correlated to the degree of intimal thickening (228) but has also been observed in patients with angiographically normal coronaries (229).

Both routine coronary angiography and IVUS may be limited in pediatric patients due to patient size and vascular access. Earlier and regular noninvasive imaging such as DSE may be required in infants and children in whom angiography or IVUS may not be possible.

9. Recommendations: Screening and diagnosis

1. Because of the diffuse nature of TCAD, IVUS is the best method for the detection of underlying TCAD. However, it is expensive, operator dependent and not available at all centres (**consensus**).
2. When IVUS is not available, coronary angiography should be performed for detection of TCAD (**consensus**).
3. A baseline assessment of graft coronary anatomy should be performed within the first year after transplantation (**consensus**).
4. Patients should be screened every one to two years for underlying TCAD. The modality used for screening may be individualized by centre according to expertise including noninvasive (DSE or myocardial perfusion imaging) and invasive methods (**consensus**).

Prevention – *Lipid lowering therapy:* Kobashigawa et al (230) provided the first evidence that statin therapy prevents accelerated TCAD. Patients were randomly assigned early after transplant to pravastatin (n=47) or no hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (n=50) and fol-

lowed up for one year. The use of pravastatin was safe, reduced the incidence of rejections associated with hemodynamic compromise, improved one-year survival and reduced the development of TCAD as assessed by IVUS (P=0.031). In this study, the development of TCAD was independent of cholesterol levels. It was postulated, therefore, that the benefit of HMG-CoA reductase inhibitors may go beyond that of cholesterol reduction.

More recently, a four-year randomized trial showed that the combination of a low cholesterol diet and simvastatin after heart transplantation led to a significantly higher long term survival rate (88.6% versus. 70.3%, P=0.05) and a lower incidence of accelerated TCAD as assessed by serial angiograms at one month after transplantation and yearly thereafter (16.6% versus 42.3%, P=0.045) (231). A subgroup of patients had IVUS performed at four years. The treated group with low density lipoprotein (LDL) cholesterol of less than 2.8 mmol/L had less intimal thickening and a lower intimal index (P=0.04). There is an increased risk of rhabdomyolysis in patients taking both statin therapy and cyclosporin. The benefit of simvastatin ws still seen eight years after transplant (232).

LDL apheresis in combination with simvastatin in patients with marked hypercholesterolemia may prove to be of added benefit (233). Referral to a lipid specialist when combination therapy is required because of severe hyperlipidemia is warranted. Treatment targeted to triglyceride levels was shown to reduce TCAD in one historic cohort (234). For resistant hyperlipidemia, conversion from cyclosporin to tacrolimus may be considered.

Calcium channel blockers: Schroeder et al (235) assessed the efficacy of diltiazem in preventing CAD after transplant. Patients were assigned to receive diltiazem or no calcium channel blocker. Baseline and two follow-up angiographic examinations were performed in 57 of 106 patients initially randomized. In treated patients who had all three angiograms, the average ± SD coronary artery diameter decreased from 2.41 to 2.19±0.27 mm at one year and 2.22 mm at two years (P<0.001). Furthermore, only two patients receiving diltiazem had coronary stenoses greater than 50% (versus 7% in the nontreated group), and nobody died (versus five in the nontreated groups). These preliminary results suggest a benefit of diltiazem in the prevention of accelerated graft atherosclerosis. No long term data have been published yet. The exact mechanisms leading to this observed reduction in progression of disease in animal and human studies are unclear. They may include inhibition of smooth muscle cell proliferation (236), improvement of endothelial dysfunction (237), potentiation of cyclosporin (238) or direct immunosuppressive properties of the calcium channel blockers themselves (239). Mehra et al (240) performed IVUS at one year in patients treated with calcium channel blockers versus those not treated and found less vascular intimal hyperplasia in the patients receiving calcium channel blockers.

ACE inhibitors: Several investigators have assessed the role of ACE inhibitors in rats with cardiac transplants. Kobayashi et al (241) found that rats treated with captopril after transplantation had less vascular rejection than the group treated with placebo. Potential mechanisms may include the ability of ACE inhibitor to decrease platelet-activating factors (242) or through its ability to block the angiotensin-1 receptor (243). ACE inhibitors may also reduce vascular intimal hyperplasia, as Mehra et al (240) showed in IVUS studies. When compared with controls not receiving ACE inhibitors, patients treated with ACE inhibitors had less vascular intimal hyperplasia.

Other agents: Experimental studies on animals have shown favourable results with the use of L-arginine (244), rapamycin (245) and angiopeptin (246). Further studies are needed to assess the efficacy of these various agents in the prevention of TCAD.

Ganciclovir, a synthetic analogue of guanine, inhibits herpesviruses both in vitro and in vivo. Recent evidence suggests that the use of ganciclovir in patients not treated with calcium channel blockers reduces the incidence of TCAD. In a post hoc analysis of 149 patients (247), followed up for a mean of 4.7 years, patients not taking a calcium channel blocker developed some degree of graft CAD in 62% of cases in the placebo group but in only 32% in the ganciclovir group (P<0.03).

Hyperhomocysteinemia is common after cardiac transplantation. Whether strategies to lower homocysteine levels have an impact on TCAD remains to be seen.

10. Recommendations: Prevention of TCAD

1. All patients should receive either pravastatin or simvastatin after cardiac transplantation (**grade A, level 1**) regardless of baseline LDL.
2. The goal LDL is less than 2.5 mmol/L (**consensus**).
3. If an antihypertensive is required, diltiazem or an ACE inhibitor should be considered first line because of possible benefits on reducing TCAD (**consensus**).

Treatment – *Percutaneous coronary intervention:* Catheter-based interventional strategies to re-establish flow in the distal bed are safe and decrease or eliminate ischemic symptoms in a majority of patients with native CAD. Percutaneous transluminal coronary angioplasty and directional atherectomy have been evaluated in transplant recipients with discrete coronary stenosis. However, they have been associated with higher procedural morbidity and mortality, as well as higher restenosis rates, than in patients with native CAD (248). Their usefulness seems therefore limited. Unfortunately, the majority of patients with TCAD may not be amenable to percutaneous revascularization.

Stenting has consistently been shown to be superior to angioplasty in patients with focal stenosis in major epicardial arteries of the native circulation. Only a few groups, to date, have evaluated coronary stenting in TCAD. No large scale studies are available. Jain et al (249) followed up 10 transplant patients who underwent coronary artery stenting between March 1994 and April 1997. Patients were eligible if they had discrete lesions (greater than 50% diameter stenosis, 12 mm or less lesion length and 3 mm or greater vessel diameter) in the proximal or midvessel without significant diffuse distal disease. These patients were followed up angiographically at six and 12 months. All patients received adjunctive antithrombotics. Angiographic success was 100% without adverse in-hospital outcome. Target vessel revascularization was required in 20% of patients and survival was 70% at 22±11 months of follow-up. Wong et al (250) compared stenting with balloon angioplasty in 12 patients. A total of 17 lesions underwent coronary stenting and 18 were treated with balloon angioplasty alone. Angiographic and procedural success was superior in the stent group (not significant) and restenosis was significantly lower

(seven of 16 versus 12 of 14, P=0.046). Heublein et al (251) documented their experience with angioplasty and stenting in 27 patients 5.7±2.9 years after transplantation. All patients received antiplatelet therapy. Patients in the stent group had better luminal gain, but 25% of stented segments still had angiographic restenosis (greater than 50%) as assessed by IVUS or angiography at six months. Therefore, stenting is feasible in selected patients with focal lesions after heart transplant and seems to have better short and long term outcomes than angioplasty.

Coronary artery bypass grafting: Similarly, coronary artery bypass grafting has been performed in a very limited number of patients. There are case reports of such successful operations in patients with severe proximal multivessel disease (252) or left main disease (253), or as an emergency procedure in patients with complicated percutaneous revascularization procedures (254). Because of the diffuse nature of the disease, coronary artery bypass grafting has, at most, an extremely limited palliative role.

Retransplantation: Selected patients with TCAD may be candidates for retransplantation; however, this is associated with a reduced long term outcome compared with primary transplantation, largely due to increased perioperative mortality (3).

11. Recommendation: Treatment of TCAD

1. For patients whose coronary anatomy is amenable, mechanical or surgical revascularization should be considered (**grade C, level 3**).

Malignancy

Malignancies are an important cause of morbidity and mortality after heart transplantation. In immunosuppressed patients, malignancies may be due to the immunosuppressive medication, chronic viral infections, or reactivation of a previous cancer that is in remission or may occur for unknown reasons, as in the general population.

PTLD: PTLD refers to all clinical syndromes associated with lymphoproliferation after transplantation, ranging from mononucleosis to malignancies containing clonal chromosomal abnormalities.

EBV is considered to have a major role in the development of most PTLD. Primary EBV infection (infection that occurs when a seronegative recipient receives an organ from a seropositive donor) conveys the highest risk for development of PTLD. Because more than 90% of the population has immunity to EBV by age 40, primary EBV infection and therefore PTLD are more common in the pediatric transplant population. PTLD in these cases can occur very early after transplantation.

Other risks for development of early PTLD are immunosuppression in particular agents such as OKT3 (84). PTLD that occurs late after transplantation does not appear to be influenced by particular immunosuppressive regimens but rather by the age of the recipient, the duration of immunosuppression and the type of organ transplanted.

Symptoms such as fevers, sweats or neurological symptoms, along with signs such as lymphadenopathy, may lead one to consider PTLD. To make the diagnosis, one must find a focus because the diagnosis and classification of PTLD are based on histological criteria. Tissue sampling must be obtained whether by excisional biopsy or needle biopsy. Testing EBV serology does not diagnose PTLD; however, EBV presence in the tumour may be helpful in guiding therapy. No staging system exists for the classification of PTLD so at present the same criteria are used to stage PTLD as are used to stage non-Hodgkin's lymphomas.

There are no controlled clinical trials comparing interventions or therapies for PTLD. The most important initial strategy is to reduce immunosuppressive therapy. This can result in regression in up to 50% of patients regardless of pretransplant EBV serostatus, clinical presentation, extent of disease or pathological features (255). With immunotherapy reduction, one must be wary of graft rejection.

Adjunctive therapy can include surgical resection or tumour debulking to manage local complications such as gastrointestinal perforation. Local radiation therapy may also be useful for certain lesions, in particular in the central nervous system.

For EBV-associated PTLD, the administration of antiviral drugs, immunoglobulin therapy or interferon have all been tried. Both acyclovir and ganciclovir have been shown to have beneficial effects in patients (256,257). Interferon-alpha, which has antiviral and antiproliferative activity, can also provide benefit in patients with PTLD (258). Unfortunately, this form of therapy appears to convey a risk of precipitating rejection and therefore careful monitoring for rejection is advised (259). Finally, there is anecdotal evidence that monoclonal antibodies may be useful to treat PTLD and are particularly attractive because of a low toxicity (260,261). Full-dose chemotherapy has also been tried with variable success. Consultation with an oncology specialist is highly recommended.

Many potential therapies exist for the treatment of PTLD. To find the best treatment or combination of therapies, randomized controlled trials need to be done. In the meantime, anecdotal evidence and case series are all we can rely upon.

In pediatric patients, routine radiological surveillance or antiviral therapy may be warranted in certain high risk patients assessed by regular interval EBV PCR (see infection section).

12. Recommendation: PTLD

1. The diagnosis of PTLD requires tissue sampling. The treatment of PTLD should consist initially of lowering immunosuppressive therapy followed by the addition of antiviral agents, monoclonal antibodies or interferon. When necessary, surgical intervention, chemotherapy or radiation therapy can be used as adjunctive therapy (**grade C, level 5**).

Skin malignancies: Skin malignancies including squamous cell carcinoma, basal cell carcinoma and Kaposi's sarcoma are the most common nonlymphoproliferative malignancies following solid organ transplantation (262-265). There is also some evidence that melanoma may also be increased in immunosuppressed patients (263). Skin cancers in immunosuppressed patients appear to be linked to duration and level of immunosuppression. Other risk factors for developing skin cancers are older age at transplantation (262), certain skin types (262,265) and exposure to ultraviolet radiation (262,265).

TABLE 6
Devices currently available* or under clinical† or animal‡ trials

Device	Type	Intended use
Implantable total artificial hearts		
CardioWest Total Artificial Heart*	Pneumatic	Bridge to transplant
Penn State Total Artificial Heart‡	Electric, transcutaneous power transfer	Alternative to transplant
AbioCor Implantable Replacement Heart‡	Electric, transcutaneous power transfer	Alternative to transplant
Implantable pulsatile ventricular assist devices		
Thoratec Ventricular Assist Device*	Pneumatic, paracorporeal in/outflow cannulae	Bridge to transplant/recovery
Thoratec HeartMate Left Ventricular Assist Device*	Electric, percutaneous power connector	Bridge to transplant/recovery
WorldHeart Novacor Left Ventricular Assist System*	Electric, percutaneous power connector	Bridge to transplant/recovery
Arrow LionHeart LVD 2000†	Electric, transcutaneous power transfer	Alternative to transplant
WorldHeart HeartSaver Ventricular Assist Device‡	Electric, transcutaneous power transfer	Alternative to transplant
Implantable nonpulsatile ventricular assist devices		
MicroMed DeBakey Ventricular Assist Device†	Electric, percutaneous power connector	Bridge to transplant/recovery
Jarvik 2000 Heart†	Electric, percutaneous power connector	Bridge to transplant/recovery
Thoratec HeartMate II†	Electric, percutaneous power connector	Bridge to transplant/recovery
Cardiac Assist Technologies AB-180 Left Ventricular Assist Device†	Electric, percutaneous power connector	Short term bridge to transplant/recovery

13. Recommendation: Skin malignancies

1. Regular dermatological evaluation is essential, as is limited exposure to ultraviolet rays (**grade A, level 1**).

Other malignancies: Other malignancies have also been documented after transplantation from single-centre experiences. Couetil et al (266) of Cambridge in the United Kingdom followed up over 300 patients over a 10-year period and documented 11 tumours of various types responsible for four deaths. In this series, no relation was demonstrated between the type of immunosuppression and tumour development. A Stanford series from 1996 described 14 cases of solid organ malignancies, again of varying types in over 600 transplants (267). Routine screening should be carried out for skin, colon, breast and cervical cancers.

14. Recommendation: Other malignancies

1. The transplant physician should be aware that a variety of solid organ malignancies may occur after transplantation. At the very least, periodic screening for malignancies must be done according to current recommendations for males and females (**consensus**) (268,269).

Other post-transplant complications – *Renal dysfunction:* Renal dysfunction after transplantation is common and often due to pre-existing renal disease, calcineurin toxicity or diabetes. Infrequently, patients require dialysis or renal transplantation. Strategies to prevent progressive renal insufficiency include a dose reduction in calcineurin inhibitor, while being wary of the potential increased risk of rejection. It is imperative that hypertension be aggressively treated in this population.

Hypertension: This is a frequent occurrence after transplantation. There are many different therapeutic strategies that can be used including ACE inhibitor or calcium channel blocker. As listed above, there are other benefits to using ACE inhibitor or diltiazem. There is no evidence in heart transplant patients that other calcium channel blockers have similar protective effects on TCAD. However, amlodipine is very effective in the treatment of hypertension. ACE inhibitors are effective; however, one must use caution because of renal toxicity and hyperkalemia. Not uncommonly, multiple agents will be required including centrally acting agents such as clonidine.

Gout: Gout is a common problem after transplantation often due to hyperuricemia associated with calcineurin inhibitors. Effective treatment often involves a short course of NSAIDs if renal function is preserved. Local intra-articular injection of steroids is also quite effective. Conversion of the patient from azathioprine to MMF allows the use of allopurinol for prophylaxis once the acute event has passed. Rarely, short term oral steroids are required, most often in polyarticular presentations and in patients with renal insufficiency. The differential for an acutely red, hot joint is infectious arthritis and this can be distinguished by aspiration of synovial fluid.

MECHANICAL CIRCULATORY SUPPORT

With the development of the first effective mechanical circulatory support device by Gibbon in 1953, there has been steady progress in the evolution of these devices to provide long term, tether-free mechanical assistance for, or replacement of, the natural heart. These have been in the form of either VADs (270,271) or total artificial hearts (272,273). Initially, the technology used pneumatic actuation to provide pumping action, but this proved to be cumbersome and restricted quality of life. The advent of electrically powered devices enabled patients to be more mobile and leave the hospital, thereby paving the way for long term, independent circulatory support. The initial goal for this technology was to provide short and medium term support for patients with heart failure. However, the ultimate goal for devices that are under development is to provide an alternative to medical therapy for patients with end-stage heart failure.

Devices for circulatory support

These devices may be classified as either pulsatile or nonpulsatile according to the type of blood flow they create (that is,

intermittent or continuous, respectively) (Table 6). Pulsatile devices use air, hydraulic fluid or a pusher plate to actuate a blood sac to cause ejection, whereas nonpulsatile devices use rotary impellers to create continuous blood flow through the device. Pneumatic systems have external compressor devices that send air to the blood pumps. Some systems require an external electrical source to provide power through a transcutaneous cable to the internal pump, while other systems send power across the skin without transcutaneous connections.

There is ongoing debate about whether pulsatility is a necessary element for nutritive blood flow. Animals have been supported without pulsatile flow for up to three months and, while the numbers are still small, the initial clinical implants of nonpulsatile systems have not identified any major problems with continuous blood flow (274-277). The nonpulsatile systems that are being tested do not have physiological responsiveness, although technology is being developed to address this limitation for future devices. Currently, changes in blood flow are accomplished by manually altering the speed of the impeller. Pulsatile systems generally respond more physiologically in that they are able to alter pump output according to pump filling.

Indications for use: The current uses of mechanical circulatory devices are to bridge patients to cardiac transplant, to bridge to recovery of the natural heart or as an alternative to medical or transplant therapy – also called 'destination therapy'. Generally for patients to be considered for one of these options, it is widely accepted that functional status and hemodynamic parameters must have seriously deteriorated acutely or chronically to jeopardize the patient's immediate or short term survival. These would include class IV CHF symptoms while on optimized medical therapy and a cardiac index less than 2 L/min/m^2 with a pulmonary capillary wedge pressure of greater than 20 mmHg while on one or more inotropic agents with or without an intra-aortic balloon pump.

A number of devices have been used for short term (less than one week) bridging such as the Biomedicus pump, Abiomed BVS 5000 and Thoratec VAD. Longer support (more than one week) may be provided by systems approved for bridging to transplant by regulatory agencies such as the Thoratec LVAD, Thoratec HeartMate left ventricular assist system (LVAS), WorldHeart Novacor LVAS and the CardioWest Total Artificial Heart. Several other systems are being developed that use either pulsatile or nonpulsatile flow but none have received regulatory approval.

Historically, bridge to recovery has referred to patients who undergo open-heart procedures, fail to be weaned from cardiopulmonary bypass and require advanced mechanical circulatory support. These patients are managed for a short time with a device but survival rates have been low, ranging from 25% to 40% (278-283). Patients often die from a combination of poor ventricular function and multiorgan failure. Current strategies include an evaluation for cardiac transplantation and support with the device until a donor heart is available. Some patients with acute myocarditis may improve while supported by devices and have the pumps removed when their hemodynamic parameters normalize (284). More recently, patients with cardiomyopathy have been supported with devices for several months and have been weaned off the devices (285-288). The offloading of the heart during support can result in some remodelling of the ventricle leading to increased contractility, the mechanisms of which are being aggressively studied (289-296). Long term outcomes of the few patients who have been weaned from their devices has been varied at best (285,297,298). The selection of patients, their management strategies while being supported and explantation criteria are being studied.

The majority of LV assist devices (LVADs) currently being implanted are as a bridge to cardiac transplantation. Unfortunately, there have been no further large registry reports on the worldwide experience since 1995 (299). Numerous centres report their results of bridge to transplant with long term outcomes being equal to nonbridged transplant patients if the patient survives the device implantation procedure (299-303). There are some data to suggest that for patients supported with devices, the outcome is better in those who were supported for a longer time, which implies that time on the device allows the patients to recover organ function and prepares them for the transplant operation (304,305).

The use of LVAD support as a bridge to retransplantation has generally been avoided because the risk of device infection is high.

Indications for LVAD use:

1. Patients with end-stage CHF on inotropic support who have either functional or end-organ deterioration or have a low probability of imminent cardiac transplantation.
2. Patients with acute heart failure (myocarditis or acute myocardial infarction) with a cardiac index less than 2 L/min/m^2 and pulmonary capillary wedge pressure greater than 20 mmHg who cannot be stabilized by either inotropic medications or surgical intervention alone.

Destination therapy

The use of LVADs as an alternative to medical or transplant therapy may provide the largest patient population for devices. But why should circulatory support devices be considered as an alternative? Although morbidity and mortality rates are quite acceptable for transplantation, a number of issues may potentially be addressed by the use of mechanical circulatory support devices (306). First, there is increasing concern over the lack of availability of donor organs. Second, the cost of a cardiac transplantation is relatively high due to the resources needed for donor and recipient procedures. Finally, infection, graft CAD and rejection are all potential complications of transplantation that may ultimately lead to the death of the patient. As an alternative, mechanical devices are available at a substantial upfront cost; however, maintenance costs are predicted to be lower than for transplant. The cost of anticoagulation is low but the potential limited durability of an artificial device is of concern because some or all of the parts of the device may need to be replaced at some time during the implantation period. Between 27% and 81% of patients with devices need some period of hospitalization during their follow-up (307,308). As the technology develops, there are continuing concerns over reliability and durability of the components, the constant surveillance by the patient required to ensure a proper power supply, and the potential for infection and other complications that are limitations of the available systems.

Because of the relatively small number of implantations in any one cardiac centre that last for more than one year, the literature on the outcomes of long term implants is rather limited. In the future, more data will be available as patient information is pooled in device registries such as with the ISHLT.

Clinical experience with long term VAD support

The largest clinical experience with long term mechanical circulatory support is with the VADs that have been approved by the Food and Drug Administration (FDA) in the United States for use as bridges to cardiac transplantation. These include the Thoratec VAD, the Thoratec HeartMate and the WorldHeart Novacor LVAS. The patients supported by these devices have generally been in end-stage heart failure, inotrope dependent and confined to hospital awaiting a transplant. These are the most severely ill of all heart failure patients. A number of centres have reported their experience with long term LVAD support with patients being discharged home to await transplantation. The Bad Oeynhausen group reported on 40 patients supported for 235.3±210 days with Novacor devices and 174.6±175 days with HeartMate devices (309). There were 15 Novacor patients and 14 HeartMate patients who were discharged home from the hospital with 19 requiring readmission for complications. Of those, more Novacor patients had neurological events (major deficits documented by CT) during home support (Novacor 30%, HeartMate 7%), while HeartMate patients had more infections (Novacor 27%, HeartMate 43%) and technical problems (Novacor 7%, HeartMate 21%). It should be noted the Novacor cannulae have been modified recently and hence anticoagulation strategies have changed, resulting in reduced thromboembolic rates.

Morales et al (308) reported Columbia Presbyterian's experience with 44 patients supported for 103±16 days by HeartMate LVADs with no deaths during their wait for transplant. However, there were infections (0.055 events/outpatient months) and device malfunction episodes (0.02 events/outpatient months) requiring treatment during support. Finally, the group from Münster reported on 16 patients discharged home (307). In-hospital support was for 86±32 days and outpatient support for 74±76 days. Again, there were readmissions for systemic or driveline infections (0.0066 events/patient days), thromboembolic events (0.0066 events/outpatient days) or device malfunction. DiBella et al (310) noted in 36 patients supported for a mean of 203.1 days that time-related analysis showed that complications occur mostly in the first three months, especially cerebrovascular events. From the published series, it is difficult to compare results for length of time supported and outcomes. What may be inferred is that there are some limitations with the current devices with regard to complication rates, but many patients may be treated as outpatients and can resume many activities of normal life.

The manufacturers of these devices are all maintaining registries of the patients supported by their devices as mandated by the FDA. Collectively, 218 patients have been supported on Thoratec, HeartMate or Novacor VADs for more than one year (October 2000 to January 2001). At this time, 34 patients are being supported, 101 have received a transplant, and 35 died while on the device. The longest duration of support was 1516 days (4.2 years) using a Novacor device. This worldwide experience supports the concept that these devices are quite acceptable in providing long term support.

Once the patient is over the convalescent phase, quality of life issues become important. Quality of life data are sparse; however, the Columbia group analyzed the quality of life of 29 patients supported as outpatients and showed that "quality of life with an LVAD was substantially better than with medical therapy, on par with renal transplantation, ... and not as good as after cardiac transplantation" (311). Although they did not make any inferences, it may be conjectured that, despite increased mobility outside of hospital, patients with heart failure supported by LVADs still face some significant restrictions before cardiac transplantation.

Clinical trials comparing mechanical support with medical therapy in end-stage heart failure

As new therapies are introduced for the treatment of heart failure, they are being scrutinized in clinical trials to prove benefit. While some older therapies such as digoxin, furosemide and heart transplantation were never subjected to randomized, double-blind control trials, physicians are requiring that new drugs and procedures be assessed as rigorously as possible. Drugs are inherently easier to test in these trials; surgical procedures are much more difficult to assess this way. The main issues affecting trials of surgical procedures are patient recruitment, technical variability between centres, physician and patient bias due to problems with blinding, and cost of the trials.

Patient recruitment into randomized trials of a procedure has been difficult due to patient expectations of the therapy. The significant differences between medical and surgical therapies and their potential outcomes are difficult for patients to accept in a trial format. If the procedure is not expected to have a major impact, then patients would tend to prefer a less invasive approach. If the procedure is expected to significantly prevent mortality, then patients would be less inclined to accept the medical alternative. It is more difficult to make procedures uniform across several centres than the administration of a drug. Technical expertise for a given procedure may vary between participating centres and may make analysis of the results difficult and extrapolation to other centres without experience once the trial is completed less valid. Physician and patient bias is a major problem due to the inability to blind trial participants to which treatment they are receiving. Expectations and outcomes may be significantly affected by this knowledge, thus limiting the validity of the results. Finally, device companies often state that they do not have the resources to mount large scale trials of their products. Therefore, remuneration for trial participation is often a major hurdle for involved centres to overcome.

Mechanical circulatory support devices have first gained acceptance in the management of end-stage, inotrope-dependent heart failure as a bridge to transplant. The next hurdle is to show that these devices can support patients with heart failure in the long term as a permanent alternative to both medical treatment and transplant. The first trial to test this approach is the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial sponsored by Thoratec Inc, manufacturer of the HeartMate LVAS (312). The patients studied were adults who had class IV heart failure on maximal medical therapy but were ineligible for transplantation for a variety of reasons. They were randomized to either LVAD support or continuing optimal medical

management. The primary objective was to determine the effect of LVAD on mortality from all causes over two years. Secondary objectives were to assess functional status, quality of life, patient preferences and cost effectiveness. The study showed that there was a 48% reduction in risk of death in the LVAD-supported group (relative risk of death 0.52, P=0.001). The medical group had a two-year survival of 8% and LVAD patients had a 23% two-year survival. Quality of life was significantly better in LVAD-supported patients by a variety of scoring indexes. LV dysfunction was the major cause of death in the medical group, whereas sepsis, failure of the device and noncardiac causes resulted in the majority of deaths in the LVAD group. These results indicate that in a group of medically treated patients at very high risk for death, LVADs can improve survival and quality of life. It may also indicate the importance of patient selection, as well as the current limitations of this device, which need to be overcome before this technology can promise a long term alternative to medical treatment or transplantation (313).

The design of an appropriate study to test the usefulness of circulatory support devices for the treatment of end-stage heart failure has been difficult (314). These first two studies should provide information regarding the natural history of patients supported by LVADs for a long period compared with medical management. Further studies will be needed to expand the indications for LVAD implantation to less unstable or high risk patients with heart failure and to define the population of patients who may benefit from LVADs.

Future directions for mechanical circulatory support

Knowing that the number of patients developing end-stage heart failure is increasing steadily, there is a great interest in providing new alternatives for treatment. With regard to mechanical circulatory support, various approaches are being assessed. Refinements to current technology are being pursued by manufacturers, and the next generations of pulsatile and nonpulsatile assist devices are being developed. In general, the main obstacles are related to provision of an adequate power supply that provides mobility but does not adversely affect quality of life. The simpler a device can be, the easier it would be to manufacture, operate and maintain. Current pulsatile systems are limited by size, power consumption, power sourcing, and difficulty to implant and repair. The nonpulsatile systems under clinical trials still have to demonstrate long term durability and reliability. Also, this technology must provide a better mechanism to control the output of the device and prevent a failure mode that compromises the patient.

Conclusion

While there is evidence that the current generation of VADs used for long term circulatory support can provide very good quality of life for the patient awaiting a cardiac transplantation, there is little information to support advocating the use of these devices as an alternative to transplantation. Clinical trials that are designed to test this indication are underway, and more information will be needed to identify the patient population who would benefit from long term support, the outcomes of long term support and the cost effectiveness of this strategy. The technology is evolving to produce devices that will be useful as an alternative to the current modalities used for end-stage heart failure. In pediatric patients, use of LVADs may be limited by patient size, and often extracorporeal membrane oxygenation is used as a bridge to recovery or transplantation. In Canada, VAD programs are in place at St Paul's Hospital (Vancouver, British Columbia), University of Alberta (Edmonton, Alberta), University Health Network (Toronto, Ontario), Ottawa Heart Institute (Ottawa, Ontario), Royal Victoria Hospital (Montreal, Quebec), Montreal Heart Institute (Montreal, Quebec), Laval University (Ste-Foy, Quebec) and the Maritime Heart Centre (Halifax, Nova Scotia).

15. Recommendations: Mechanical circulatory support

1. Patients with end-stage heart failure who have a rapid deterioration or who are not responding to therapy and may undergo transplantation imminently should be considered for circulatory support by a total artificial heart or VAD (**consensus**).
2. Centres with cardiac assist programs should participate in a data registry to assess the effectiveness of the therapy and its use as destination therapy (**consensus**).

XENOTRANSPLANTATION

Xenotransplantation is the transfer of living cells, tissues or organs from one animal species to another. Xenotransplantation has been gaining in interest because of the current crisis in organ donation. There is an increasing number of patients being listed for transplant that far outstrip organ donation. What are the possible solutions? As previously mentioned, the first is to increase organ donation. However, it has been estimated that even with optimal organ donation including such initiatives as 'presumed consent' and institutional and donor family financial incentives, there will still not be enough to meet demand (4). Use of suboptimal donors is being explored; however, these would fail in time and increase the numbers of patients with a failing transplant who would likely benefit from retransplant were there an unlimited supply.

This has led to a search for alternative sources of organs. Xenotransplantation may provide an unlimited source of organs, cells and tissues. Surgery would be scheduled allowing patients to undergo transplantation before becoming critically ill from end-organ disease.

The current best results in pig to nonhuman primate transplantation are limited by hyperacute and acute vascular rejection with a median survival of two to 12 days with no primate living longer than 78 days (315-317). The best result with a baboon to human xenotransplant was baby Fae, who survived 20 days after transplant (318). The white paper from the ISHLT requires "60% survival of life-supporting pig to nonhuman primate transplants for a minimum of three months in a series of consecutive experiments with a minimum of 10 animals surviving for this period of time" (4).

The transplantation of cells, tissues or whole organs across species raises concerns of potential transmission of known infectious organisms. Historically, we know that animals have served as reservoirs for infectious diseases that have caused deadly epidemics. During the influenza outbreak in 1918, thought to be secondary to a porcine virus that was transmitted from pigs to humans, it was estimated that 20 to 40 million people died (319,320). Screening for known pathogens and raising animals in a pathogen-free environment may reduce

the risk. However, there are concerns that organisms that have not been infectious in humans will become so because inserting the animal organ directly into a human breaks down natural barriers preventing infection. The genetic modification meant to reduce organ rejection may lead to the development of new infectious agents or increase the virulence of a known infectious agent. Immunosuppression required to prevent rejection would likely increase the infection risk.

One major concern relates to porcine endogenous retroviruses (PERV) that are part of the pig genome and are thus inheritable and difficult to eradicate. PERV has been shown to infect human cells and cell lines in vitro (321,322) raising concern of infection after xenotransplantation. However, a small study of 36 patients on immunosuppressive therapy showed that 97% of patients exposed to porcine tissue had no evidence of persistent PERV infection, although a significant number had persistent circulating pig cells (323).

The risk is not isolated to the recipient but also applies to the immediate family, caregivers, general public and potentially subsequent generations because of inheritable transmission. There must be measures in place to monitor lifelong not only the recipient but also the close surrounding community, for example, the health care provider and immediate family. Privacy and confidentiality will likely be signed away with consent in order to allow monitoring of close contacts who themselves will have to give consent to ongoing monitoring (324).

Registries will need to be in place on both national and local levels to adequately screen, discover and detect new infectious agents, as well as to bank tissue for future analysis (325-328). Animal concerns range from the humane treatment and genetic modification of animals to determining our right to use animals to prolong human life (328).

There are complex legal, social, economic, health and ethical issues surrounding xenotransplantation (329). Canada held a public consultation to determine opinion on whether Canada should proceed with xenotransplantation. Canadians felt that we should not proceed with xenotransplant at this time (www.xeno.cpha.ca).

COST

Economic burden of heart failure admissions

Improved management of acute cardiac conditions and better treatment options for CHF have resulted in a significant increase in the number of patients with CHF requiring admission to hospital. CHF has surpassed acute myocardial infarction as the leading cause of cardiac hospital admissions in Canada (330). In Ontario the average annual hospitalization rate is 287/100,000 population with an average length of stay of 7.3 days and an average 30-day readmission rate of 25% (331). It is estimated in 1998 dollars that the direct cost for these admissions totalled US$20.2 billion. Even as early as 1991 these costs exceeded the costs of all cancers and myocardial infarctions combined (332).

Treatment of CHF includes pharmacological therapies, nonpharmacological therapies and interdisciplinary care, all of which have been extensively analysed and shown to be cost effective (332).

In the later stages of heart failure, however, more expensive technologies have been used to manage patients. LVADs have been shown to be more expensive than intravenous inotropic plus intra-aortic balloon pump therapy in one study (333), while having a lower daily hospital charge in another study (334). Selection bias and differences in cost determination limit the interpretation of these studies (335).

Like a heart transplant, the implantation of LVADs is costly as an initial expense, but unlike transplants, LVAD patients do not require expensive antirejection drug therapy or diagnostic interventions. However, centres with a large experience in outpatient LVAD follow-up indicate that about 27% of outpatients require readmission for complications such as infection and device malfunction (308). As totally implantable and more reliable devices become available, these complication rates should decrease. Costs of long term LVAD support have been estimated to be US$219,139 over the first year (336) and CAN$201,576 for three months (337). When used as a bridge, LVADs almost double the cost of transplantation. This is a less cost effective approach; however, LVADs result in an over 70% survival in these patients at highest risk for dying while waiting for a donor heart. However, there are no data that imply a cost difference between LVADs as destination therapy and transplantation.

Direct costs of transplantation

Direct costs include services rendered such as hospitalization costs, diagnostic tests, procedures, medications, office visits and rehabilitation costs. Assessment of costs, however, is often difficult because resources such as personnel space, equipment, depreciation and shared goods cannot be easily accounted for. In light of this, many studies look at 'charges' as a surrogate for costs, but it is important to understand that this often significantly underestimates the true costs of the procedure.

Limited data exist related to the cost of transplantation within Canada; however, studies from various centres around the world have shown that the median cost for heart transplantation in the United States in 1998 dollars was US$91,570 with a range from US$10,795 to as high as US$1,465,640 (338).

Indirect costs of transplantation

Indirect costs include loss of income as a result of illness, travel expenses and the cost for specialized care services. In addition there are intangible costs such as physical and emotional pain and suffering. Most analyses of costs of heart transplantation are unable to adequately address these indirect costs. Estimates on return to work have ranged from 21% to 87% but a more recent analysis suggests 69% of transplant recipients remain employed for five years or more (339).

Cost effectiveness of transplantation

Much attention was focused in the early 1990s on the cost effectiveness of cardiac transplantation relative to other medical and surgical procedures and was summarized in an American College of Cardiology task force report (340). These studies suggest that the incremental cost effectiveness ratio of heart transplantation ranges from US$25,000 to US$44,300 per year of life gained (341), which has been defined as an acceptable ratio (342). There is very little information related to the cost of transplantation in Canada, but the issue has become a focus of public interest both in Canada (343) and abroad (344).

Significant costs are also incurred in the first five years after transplantation. An attempt to model these cost has been made (345).

Many factors also have the potential to affect the cost of transplantation in the future. Changes in listing criteria (346), patient and donor demographics (5), and increased use of assist devices can affect costs. Improved immunosuppressive and other pharmacological agents (5), modified isolation procedures (347) and improved median survival (348) can decrease costs.

The costs associated with cardiac transplantation are high and as the health dollar becomes scarce considerable debate exists as to whether these costs are justified (349). Transplantation costs also raise significant ethical issues that are beyond the scope of this document but are addressed elsewhere (349,350).

Retransplantation

The costs of retransplantation are much higher than the primary transplantation(US$89,394 versus $112,450), while the one-year survival rate is less (83.3% versus 60.9%) (9). Consequently there has been significant debate regarding whether retransplantation is cost effective and even whether it should be performed on ethical grounds (351).

Summary: Cardiac transplantation is an expensive medical treatment modality that is clearly effective in improving symptoms and prolonging the life of patients with end-stage heart failure. Often it is the only remaining survival option for these patients. Furthermore, cardiac transplantation is a cost effective procedure in comparison with other medical technologies used routinely in Canadian practice. Many factors have the potential to significantly alter this cost effectiveness ratio and therefore the costs of cardiac transplantation require a more contemporary, comprehensive and ongoing analysis.

16. Recommendations: Costs

1. Further research should be done within Canada to ascertain the total costs associated with cardiac transplantation, including both pre- and post-transplant care in the contemporary health care environment (**consensus**).
2. Standardized methods should be developed to compare the incremental cost effectiveness ratio of cardiac transplantation with other major medical and surgical procedures (**consensus**).
3. Attempts should be made to fairly incorporate indirect costs and quality of life issues into any future cost effectiveness analysis (**consensus**).

CONCLUSIONS

The most important current limitation to organ transplantation is donor availability. In 2000, of 591 potential donors in Canada, only 475 actually became organ donors, of whom only 171 became heart donors (see www.chi.ca). During the same period, 25% of patients with heart failure on the waiting died.

The organ donation rate in Canada is 15.4 donors per million population. This differs significantly from other countries including the United States. Given this low organ donor rate, it is necessary to put special emphasis on increasing organ procurement activity. There must be increased public awareness of organ donation and transplantation. The donor family is crucial to the process of donation; therefore, education and awareness campaigns should be implemented to encourage citizens to discuss with their families their decision to donate an organ. Increased efforts should be placed on the early identification of potential donors (352).

Cardiac transplantation is the accepted therapy for end-stage heart failure when maximal medical and surgical therapy fails. It is imperative that optimal heart failure therapy be instituted and aggressively managed (353). As a result of advances in organ preservation, immunosuppressive therapy, improved surgical technique, antihypertensive therapies and routine statin use, outcomes have continued to improve (3). However, cardiac transplantation remains a treatment and not a cure. Given current organ shortages, ongoing efforts must be made to improve organ donor rates and seek alternatives to transplantation. LVADs appear to be the most promising. Xenotransplantation raises significant concerns related to unknown infection risk and serious ethical and legal issues. At the moment stem cell therapies remain in the research arena. The potential therapeutic modalities being developed promise to change the face of heart failure management over this next decade.

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