Canadian Cardiovascular Society Consensus Conference update on cardiac transplantation 2008: Executive Summary

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The Canadian Cardiovascular Society published its Consensus Conference on cardiac transplantation in 2003 (1). The present Executive Summary provides an update on the previous document, with a focus on new evidence and significant changes in our understanding of relevant issues and management of cardiac transplantation. The standard guidelines used in these recommendations are shown in Table 1.

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 and expert opinion

INDICATIONS AND CONTRAINDICATIONS FOR CARDIAC TRANSPLANTATION

Cardiac transplantation is the treatment of choice for patients who have severe end-stage heart failure despite maximal medical therapy and/or complex congenital heart disease not amenable to surgical palliation at reasonable risk. With improvements in organ preservation, antirejection regimens and post-transplant management, survival rates following cardiac transplantation are very good. Unfortunately, there is an ever-enlarging gap between the supply and demand for transplantable organs, a gap that is made more severe by expanding indications and less conservative listing criteria for cardiac transplantation. The listing criteria and indications for cardiac transplantation have been reviewed by the International Society for Heart and Lung Transplantation (ISHLT) (2) and outlined in a Canadian consensus document on cardiac transplantation that was published in 2003 (1). In the context of these new guidelines, the following issues have been updated.

Indications

In general, cardiac transplantation can be considered in patients with late-stage heart disease who have received optimal medical and surgical (if appropriate) therapy, and who have an unacceptable quality of life and poor anticipated survival. Typically, this includes patients with late-stage heart failure, refractory life-threatening arrhythmias despite optimal medication, surgical and device therapy, and complex congenital heart disease with failed surgical palliation or not amenable to surgical palliation at an acceptable risk.

Functional class: The presence of a severely decreased left ventricular (LV) ejection fraction or a history of functional class II to IV heart failure alone are insufficient indications for cardiac transplantation. Risk stratification should extend beyond assessment of functional class. Patients with recent heart failure hospitalizations are at higher risk for cardiac death (3). The 6 min walk test may also be helpful for risk stratification (4). The biomarker B-type natriuretic peptide has been shown to provide important prognostic information in heart failure patients (5-10), with high baseline values or increasing values over time being associated with decreased survival.

Assessment of functional capacity by respiratory gas analyses: Exercise testing with gas exchange analyses (cardiopulmonary exercise testing) is routinely used as an objective assessment of functional limitation and prognosis. The exercise test can be performed on a treadmill or a bicycle. The ramp protocol appears particularly well suited to assess patients with advanced disease (11). Since the previous consensus statement, there have been some changes in the indication for cardiac transplantation in relation to the oxygen uptake (VO_2) achieved. An absolute indication includes a peak VO_2 of less than 10 mL/kg/min with achievement of the ventilatory threshold. Relative indications include patients with peak VO_2 between 11 mL/kg/min and 14 mL/kg/min or less than 55% of the predicted value for the age group. Transplantation is not recommended for patients with a peak

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VO_2 higher than 15 mL/kg/min without other indications for transplantation. The recent publication from the ISHLT (2) also suggests lowering the threshold for transplantation to less than 12 mL/kg/min for patients treated with beta-blockers. Cardiopulmonary exercise testing results alone, however, do not constitute candidacy for transplantation, and must be used in conjunction with a complete clinical assessment.

Heart failure survival score: The heart failure survival score may be used to evaluate prognosis and assess candidacy for transplantation. The heart failure survival score is a predictive model using seven clinical characteristics, and can stratify patients into low, medium and high risk for poor transplant-free survival (12). These variables include the presence of ischemic etiology of heart failure, resting heart-rate value, LV ejection fraction, mean arterial blood pressure, presence of intraventricular conduction delay, peak VO_2 value and serum sodium level.

Contraindications

Pulmonary hypertension: The presence of significantly increased pulmonary artery (PA) pressure is a critical issue in the determination of candidacy for cardiac transplantation. The potential for right heart failure is significant in the early postoperative stages of cardiac transplantation in the presence of refractory elevation of PA pressure. Before a patient can be listed for cardiac transplantation, right heart catheterization is mandatory to assess PA pressure and identify whether high PA pressures are reversible with therapy. Attempts to reverse pulmonary hypertension should be undertaken when the PA systolic pressure is more than 50 mmHg, and when either the transpulmonary gradient (the difference between the mean PA pressure and the PA wedge pressure) is more than 14 mmHg or when the pulmonary vascular resistance (PVR) is more than 3 Wood units (while maintaining a systolic arterial pressure of 85 mmHg) (1,2). Continuous infusion of intravenous (IV) inotropes and/or vasodilators, inhaled nitric oxide, or the administration of phosphodiesterase-5 inhibitors such as sildenafil may be used (13). Pulmonary hypertension is considered a relative contraindication to cardiac transplantation when PVR exceeds 5 Wood units. PVR greater than 6 Wood units or a transpulmonary gradient exceeding 16 mmHg, or the absence of a decrease in pulmonary resistance to less than 2.5 Wood units in response to vasodilatory challenge should be considered an absolute contraindication to transplantation. An increasing number of patients with initially refractory pulmonary hypertension have been bridged to transplantation using mechanical circulatory support to facilitate reversibility of high PA pressure (14,15).

Other contraindications: The contraindications outlined in the previous consensus document remain valid. In general, patients with extracardiac disease that would significantly reduce their expected lifespan, or that would be exacerbated by the post-transplant use of immunosuppressive agents, are not candidates for transplantation, nor are patients without significant rehabilitation potential.

DONOR MANAGEMENT

The rate of organ donation continues to be insufficient to meet the increasing demand for donor hearts. One of the main steps proposed to improve procurement and transplant activity is education of the general public and health care professionals. As such, an ongoing training program for health care professionals should be present in every medical institution to improve the identification and management of potential donors using standardized protocols (16-18). The importance of organ donation, signing donor cards and discussing one's organ donation wishes with family members are key components in the education of the public.

The United Network for Organ Sharing (USA) reported only a 42% donor yield in 1998 (19). In Canada, similar donor yields have been reported, with a heart donation yield as low as 39% (20). Clinical efforts to improve donor management have traditionally focused on hemodynamics. The overall goals are to achieve euvolemia, to adjust vasoconstrictors and vasodilators to maintain normal afterload, and to optimize cardiac output without relying on high doses of inotropes, which increase myocardial oxygen demand. Although echocardiography is effective in screening for anatomical abnormalities of the heart, the use of a single echocardiogram to determine the physiological suitability of a donor is not always sufficient. In fact, serial echocardiography may be necessary to evaluate resuscitation efforts to rescue organs and allow for their use (19). The Papworth Hospital transplant program in Great Britain has been a pioneer in the field of resuscitating donor hearts. The donor yield was increased substantially by using a PA catheter to guide physiological assessment and management of ventricular dysfunction (21). The investigators suggested an aggressive approach to donor management including invasive monitoring with PA catheters and onsite resuscitation under the guidance of an experienced cardiac intensivist. More recent work from the same group has been aimed at developing tools to identify subclinical right ventricular (RV) dysfunction present in donor hearts, a condition that is well known to adversely affect transplant outcomes (22,23).

The importance of hormonal resuscitation in increasing donor yield has become clear and was the focus of a recent consensus conference report on improving organ donation (18). Hormonal resuscitation consisting of donor infusions of combined glucose, insulin and potassium, triiodothyronine, cortisol and arginine vasopressin have been shown to reduce donor inotropic requirements and improve recipient outcome following transplantation, and were recommended in a recent consensus statement (19,24).

Recommendation

- Hormonal replacement for potential cardiac donors (grade B, level 2).
  - Triiodothyronine: 4 µg bolus then continuous infusion at 3 µg/h.
  - Arginine vasopressin: 1 U bolus then continuous infusion at 0.5 U/h to 4 U/h (titrate to systemic vascular resistance of 800 dyn•s/cm^5 to 1200 dyn•s/cm^5.
  - Methylprednisolone: 15 mg/kg bolus.
  - Insulin: 1 U/h (titrate to maintain blood sugar of 6 nmol/L to 10 nmol/L).

Recipient status and donor allocation

When patients have been listed for transplantation, they are assigned a listing status according to their disease stability and the likelihood of survival without transplantation. Status criteria have been developed by the Canadian Cardiac Transplant Network (CCTN) for listing of cardiac transplant recipients across the country (25,26). The highest priority patients (status 4) are those who are mechanically dependent (on mechanical circulatory support or ventilatory support) and intensive care unit-dependent. Status 3.5 patients are those on high-dose or multiple inotropes in the hospital, highly sensitized patients and those with acute refractory life-threatening arrhythmias. Status 3 patients include those with ventricular assist devices (VADs) in the absence of complications, patients on single, low-dose inotropes in the hospital, adult congenital heart disease patients who are arterial shunt-dependent or who have a resting oxygen saturation of less than 65%, and those with complex congenital heart disease and increasing dysrhythmic or systemic ventricular decline. Heart and lung recipients are also status 3. In-hospital patients, patients on outpatient inotropic therapy and adult congenital patients with a resting oxygen saturation of 65% to 75% or those with Fontan palliation and protein-losing enteropathy, as well as patients listed for multiple organ transplantation (other than heart and lung) are considered status 2. All other out-of-hospital patients are considered status 1.

The CCTN has endorsed and formalized a system whereby donor hearts are allocated nationwide to the patients most in need of transplantation. A nationwide list is distributed to all organ procurement

organizations (OPOs) across Canada, on which patients are identified according to their listing status. The principle of the organ-sharing agreement, as outlined by the CCTN, is as follows (25):

> The OPO will offer the donor heart to the Canadian site with the highest status recipient in the geographic area. The OPO will also notify the Canadian program(s) with a potentially appropriate Status 4 recipient(s) nationwide of the potential donor heart. If there are competing potential recipients, mandatory discussion in a timely fashion, physician to physician, will ensue to allocate the organ, the principle being that the recipient with the longest current listing as Status 4 be given priority. If consensus is not reached, final allocation will be made by the center to which the heart was originally offered.
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> All out-of-country donor hearts will be offered nationally to all programs with eligible Status 4 recipients. If there are competing Status 4 candidates, mandatory discussion is required in a timely manner, physician to physician, prior to allocation of the donor heart. If consensus is not reached, final allocation will be made by the centre with the recipient with the longest current listing time as Status 4.

RECIPIENT MANAGEMENT

The highly sensitized patient

The presence of donor-specific cytotoxic antibodies to human leukocyte antigen (HLA) in patients who are waiting for cardiac transplantation is referred to as humoral sensitization. Transplantation of sensitized recipients is associated with significant risk for early graft failure and reduced survival as a result of humoral rejection (27,28). Recognition and measurement of the degree of sensitization to HLA antigens is an important part of the evaluation of transplant candidates. In the renal transplant population, prospective lymphocyte cross-matching is routinely performed; however, prospective donor-recipient cross-matching is often not feasible for thoracic transplantation. The degree of sensitization of cardiac transplant recipients is most commonly assessed by testing the sera of prospective recipients against a panel of lymphocytes known as the panel-reactive antibody (PRA) screen (29). A PRA higher than 10% is considered to represent sensitization. PRA determination using lymphocyte cytotoxic antibody screening (complement-dependent cytotoxicity) is less accurate in the detection of truly sensitized patients than screening using flow cytometry (30). Although high-precision HLA antibody testing may increase the wait time for some patients because it is more likely to identify them as sensitized than other methods, the consensus recommendations from the Canadian Council for Donation and Transplantation indicate that this should lead to better outcomes for patients overall and is therefore an acceptable compromise.

Elevated PRA titres are found more frequently in patients with a history of multiple transfusions and previous allograft transplant, and in multiparous women. Elevated PRA has more recently been identified in patients with VADs (31). As such, the proportion of highly sensitized patients on cardiac transplant waiting lists has been progressively increasing with the expanding proportion of heart transplant patients bridged using VADs. The mechanism responsible for the increased production of HLA antibodies in VAD patients is likely multifactorial and includes T cell deregulation with prominent B cell activation. Recipients of VADs who do not receive blood products may become fully sensitized because of an immunological reaction at the blood-VAD interface (32).

Treatment strategies aimed at lowering PRA have been proposed; however, to date, no guidelines have been published. Studies have suggested that pooled human IV immunoglobulin (Ig) is effective in reducing allosensitization and can safely lower PRAs (33). A commonly reported regimen consists of monthly treatment with IV Ig at a dose of 2 g/kg. However, not all sensitized patients respond to IV Ig alone. Plasmapheresis has been used to reduce HLA antibody alloreactivity with variable success. The limitations of plasmapheresis are that multiple treatments may be necessary to achieve low circulating IgG levels; this may not be tolerated hemodynamically, and the onset of action may be later than what is seen with IV Ig. It has been suggested that plasmapheresis may be associated with a high frequency of infectious complications. Despite the above limitations, some centres advocate a combination of IV Ig and plasmapheresis to reduce PRA. While the above therapies are aimed at circulating antibodies, cyclophosphamide has been used to suppress the immune response by inhibiting DNA replication, cell division and proliferation, and appears to have a specific effect on B cells (34). The rationale for cyclophosphamide is to prevent a possible rebound in B cell proliferation after therapy with IV Ig or plasmapheresis. More recently, rituximab, a chimeric murine anti-CD20 antibody, was shown to reduce antibodies against prospective donors in select potential renal and cardiac transplant recipients (35,36). Studies are ongoing to determine the efficacy of this therapy in reducing PRA in patients awaiting transplantation with elevated PRA. While no consensus exists, it appears that a regimen of IV Ig with cyclophosphamide is superior to plasmapheresis for the reduction of allosensitization and shortens the waiting time to cardiac transplantation in sensitized patients. The use of anti-CD20 therapy is promising.

RV dysfunction

RV dysfunction is a significant cause of primary graft failure that represents up to 50% of early complications and 42% of early deaths following heart transplantation (37,38). There is no single best approach to the treatment of RV failure. The overall goals of the therapy are to maximize coronary perfusion, reduce preload of the ischemic distended RV, decrease RV afterload (reducing PVR), optimize oxygen delivery and limit oxygen consumption. There is sufficient centre-to-centre variability in the approaches to acute RV failure to make it difficult to obtain a consensus. Initially, the maintenance of atrial contraction through either atrial pacing or isoproterenol hydrochloride infusion (10 ng/kg/min to 70 ng/kg/min) is important to aid in filling the acutely decompensated RV. Neither atropine nor neostigmine have been found to be useful in the transplanted heart. Inotropic support by the usual adrenergic agonists may be used initially in an effort to improve RV contractility. Assiduous avoidance of hypercapnea and acidemia will prevent further increases in PVR through vasospasm. Pharmacological attempts to induce pulmonary vasodilation are recommended and may include inhaled nitric oxide, IV milrinone, prostaglandin E1 and sodium nitroprusside. Compared with IV prostaglandin E1, inhaled nitric oxide was shown to be more effective in reducing PVR with minimal effect on systemic vascular resistance (39). Alternatively, an inhaled prostaglandin preparation (iloprost) has been used successfully in reducing PVR with minimal systemic vasodilation (40). In patients with severe RV dysfunction unresponsive to medical management, mechanical circulatory support should be considered early before irreversible end-organ dysfunction occurs. As a first-line approach, intra-aortic balloon counterpulsation may be useful in the management of patients with acute RV failure, likely by improving coronary perfusion and LV performance, thus indirectly enhancing RV function (41). While many VADs are commercially available, significant debate remains regarding the best mechanical support for RV dysfunction following heart transplantation. In a small, single-centre study (42), extracorporeal membrane oxygenation was found to result in significantly higher organ survival but not patient survival compared with a mechanical right VAD.

Recommendations

- The goals of management of RV dysfunction are to maximize coronary perfusion, reduce preload of the ischemic distended RV, decrease RV afterload (reducing PVR), optimize oxygen delivery and limit oxygen consumption. This may be accomplished by multiple strategies including pulmonary vasodilation (grade A,

level 1) and early consideration for mechanical support (grade B, level 2).

IMMUNOSUPPRESSIVE THERAPY

The goal of post-transplant immunosuppressive therapy is to prevent the occurrence of allograft rejection while minimizing toxicity, and infectious and malignant complications.

Induction therapy

Despite more than two decades of clinical experience in the calcineurin inhibitor (CNI) era, controversy still exists regarding the beneficial or detrimental role of induction immunosuppression as an initial immunosuppressive strategy following cardiac transplantation (38,43,44). The use of such agents evolved from the intuitive assumption that intense immunosuppressive therapy is needed early after transplantation to prevent acute rejection and as a means of avoiding early high-dose CNI therapy and the potential risk of nephrotoxicity (1,43).

The range of induction agents clinically available and studied in cardiac transplantation includes antilymphocyte (depleting) antibodies such as polyclonal antithymocyte globulins (ATGs) (ATGAM [Pfizer Inc, USA] and rabbit ATG) and the monoclonal anti-CD3 antibody OKT3 as well as the anti-interleukin-2 (IL-2) receptor (non-depleting) antibodies daclizumab and basiliximab (45).

The use of antilymphocyte antibody therapy is well detailed in the "2001 Canadian Cardiovascular Society Consensus Conference on Cardiac Transplantation" (1) and the conclusions are still valid. However, since the publication of this document, the literature examining the use of anti-IL-2 receptor antibody therapy (46-51) has grown. As is the case with most studies of immunosuppression in cardiac transplant recipients, study design flaws and small patient numbers limit the interpretation and generalizability of these results. However, data from the accumulated literature suggest the following:

- Many centres successfully avoid induction immunosuppression with no evidence of significant adverse outcomes (38,43,44).
- Induction therapy may be beneficial in subgroups of patients (1,38,43-45) such as those with significant renal or hepatic dysfunction, those in whom maintenance immunosuppressive therapy will be delayed, or in patients at higher risk for rejection (the sensitized patient).
- The use of OKT3 and ATG (but not anti-IL-2 receptor antibodies) may increase the risk of lymphoma in the first year after solid organ transplantation (46).
- ATG and IL-2 receptor antagonists, if needed, are preferable to OKT3 (1,46). The use of OKT3 confers no survival advantage and results in a definite excess of infectious complications, malignancy and general adverse effects (eg, cytokine release syndrome). The use of OKT3 as induction therapy has diminished dramatically in the past five years (42).
- The use of ATG compared with IL-2 receptor antagonists results in similar survival outcomes (47-49). ATG use may be associated with less biopsy evidence of rejection but results in more infectious complications.
- IL-2 receptor antagonists reduce biopsy evidence of rejection compared with no induction therapy (50,51), although no survival advantage has been demonstrated. Higher rates of life-threatening infection have been observed when IL-2 receptor antagonists are combined with ATG for rejection therapy (50). The use of IL-2 receptor antagonists has increased significantly over the past five years, likely due to the low incidence of acute adverse effects.

Maintenance therapy

Combinations of immunosuppressive agents have been used in an individualized approach to achieve this goal. CNIs, purine antimetabolites and steroids are the most commonly used agents. The mechanisms of action and adverse effects of these agents are detailed in the previous consensus document (1).

CNIs: Preliminary studies suggest that 2 h post-dose blood cyclosporine concentration monitoring may be associated with reduced acute rejection and less renal impairment than trough-level monitoring (52,53). However, the superiority of this monitoring strategy remains controversial.

Two prospective, open-label, randomized clinical trials recently examined the efficacy of tacrolimus in cardiac transplantation. The results of an American trial (54) in 343 patients suggest that the combination of tacrolimus plus mycophenolate mofetil (MMF) offers advantages over either tacrolimus plus rapamycin or cyclosporine plus MMF, including a lower incidence of treated rejection, less hypertension, less hyperlipidemia and less renal insufficiency. A European trial (55) in 314 patients randomly assigned to receive either tacrolimus or cyclosporine in combination with azathioprine and corticosteroids demonstrated that tacrolimus-treated patients had fewer treated rejections, and less hypertension and hyperlipidemia, but more new-onset diabetes mellitus.

Steroid withdrawal: Recent larger studies have confirmed the results of earlier smaller studies; that steroid withdrawal is safe in a majority of low-risk patients (56,57). A significant number of patients, however, required reintroduction of steroids. Both studies showed a trend toward better survival in patients successfully weaned off steroids. This, however, may reflect a subgroup of patients who are themselves immunologically privileged.

Purine synthesis inhibitors: A long-term follow-up study of the first randomized MMF heart study (58,59) has confirmed that the benefits associated with this agent extend to three years following transplantation, with reduced graft loss due to rejection and a 36% reduction in overall mortality. A re-analysis of the intravascular ultrasound data from this trial also showed less progression of allograft coronary artery disease (ACAD) (60).

Target of rapamycin inhibitors (proliferation signal inhibitors): The target of rapamycin (TOR) inhibitor, everolimus, was compared with azathioprine in a two-year multicentre, randomized trial in 634 de novo heart transplant recipients who were also receiving cyclosporine and steroids (61). At 12 months, both doses of everolimus were associated with a lower incidence of efficacy failure and acute rejection compared with azathioprine, and the incidence of ACAD was significantly lower. The 48-month follow-up results of this trial demonstrated fewer rejections in the everolimus-treated patients (62). A smaller trial of rapamycin (63) in de novo transplant patients also showed fewer rejection episodes and less coronary allograft vasculopathy. To date, none of the TOR inhibitor trials in heart transplantation have demonstrated increased survival. Safety concerns include increased rates of some types of infection. Wound healing may be a concern with sirolimus and, perhaps, everolimus. Co-administration of TOR inhibitor and CNI can exacerbate CNI-related nephrotoxicity.

Practical tip

- When adding a TOR inhibitor, the CNI dose should be decreased to reduce nephrotoxicity.

Recommendations

- 2 h post-dose blood cyclosporine levels may be used instead of trough levels (grade B, level 2).
- MMF should be used instead of azathioporine (grade A, level 1).
- Steroid withdrawal may be considered in most patients (grade B, level 2).
- TOR inhibitor may be considered for patients with ACAD (grade C, level 3).
- Tacrolimus may be considered instead of cyclosporine in patients who have refractory rejection (grade B, level 2).

POST-TRANSPLANT COMPLICATIONS

Acute rejection

The details of the mechanisms of graft rejection were described in the first consensus document (1). The frequency of cellular rejection and

hemodynamic evidence of rejection has decreased and it is currently not uncommon to see significant cellular rejection in the absence of hemodynamic changes, and vice versa. A hemodynamic deterioration in the absence of typical histological evidence of acute cellular rejection may occur in as many as 10% to 20% of cardiac allograft recipients. Microvascular immune-mediated injury may be present in the absence of cellular infiltrate and necrosis, and likely mediates cardiac allograft dysfunction and injury in many of these cases. This is referred to as humoral or antibody-mediated rejection (AMR). AMR is associated with a significantly worse survival rate and predisposes patients to coronary vasculopathy (64).

The ISHLT grading system (Table 2) was recently revised to reflect the shift in clinical response to lower grades of rejection and provide recommendations for the histological recognition and immunohistological investigation of acute AMR (65,66).

Recommendations

- RV endomyocardial biopsy, performed under fluoroscopic or echocardiographic guidance, remains the gold standard for surveillance and detection of early cardiac allograft rejection (consensus).
- The 2004 revised ISHLT standardized grading system for histological assessment of endomyocardial biopsy 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 endomyocardial biopsy for rejection (consensus).
- Immunohistochemical assessment of biopsy samples is recommended if there is clinical evidence of acute graft dysfunction in the absence of cellular rejection, or if there are histological features of AMR on the biopsy. Patients with histological AMR or hemodynamic compromise should also be assessed for circulating antibodies (consensus).
- Assessment of LV function by either echocardiography or angiography should be performed in patients with suspected or biopsy-proven rejection to rule out hemodynamically compromising rejection (consensus).

Treatment of cellular rejection: The management of cellular rejection is discussed in detail in the previous consensus document, and the previous recommendations remain valid.

Treatment of humoral rejection or AMR: This type of rejection is more severe, is often resistant to standard forms of rejection therapy and is associated with a worse prognosis than cellular rejection (64). Treatment protocols using high-dose steroids, cyclophosphamide and plasmapheresis have been associated with improved survival and graft function. Small studies have used high-dose human IV Ig as an effective treatment for humoral rejection in renal and cardiac transplant recipients. Most commonly, IV Ig is used in combination with plasmapheresis.

Recommendations

- Recommendations for the management of acute cellular and humoral rejection documented in the previous consensus statement remain valid.

Practical tips

- Acute rejection associated with hemodynamic compromise or occurring within the first 30 days post-transplantation requires more aggressive therapy regardless of grade.
- Patients with symptomatic or asymptomatic reduction in ventricular function should be assessed for the presence of acute rejection and ACAD.

Infections

Immunosuppressed patients are at increased risk for infectious complications post-transplantation. The types of infections that can occur during the post-transplant period and their management were covered extensively in the previous consensus document (1).

TABLE 2
Revised (R) International Society for Heart and Lung Transplantation grading system for antibody-mediated rejection (AMR)

Grade	Definition
0 R	No rejection
1 R (mild)	Lymphocytic infiltrate, with up to one focus of myocyte necrosis
2 R (moderate)	2 or more foci of infiltrate with associated myocyte damage
3 R (severe)	Diffuse inflammatory process + multifocal myocyte necrosis ± edema ± hemorrhage ± vasculitis
Humoral rejection	Positive immunofluorescence, vasculitis or severe edema in the absence of cellular infiltrate recorded as additional required information
AMR 0	Negative for acute AMR: No histological or immunopathological features of AMR
AMR 1	Positive for AMR: Histological features of AMR, positive immunofluorescence or immunoperoxidase staining for AMR (positive CD68, C4d)

Data from references 65 and 66

Practical tips

- The diagnosis and management of infections can be complex, and consultation with local infectious diseases specialists is recommended.
- Identification of the etiological agent of infection is extremely important and early aggressive testing should be considered when the diagnosis is not immediately apparent or in patients who fail to respond to initial empirical therapy.
- Dual or sequential infection is common and the initial presentation may be atypical due to a blunted immune response.

Prevention of infections: Infection prevention begins with obtaining donor and recipient history, and physical examination to identify risk factors for existing and latent infections. Serological screening for donors and recipients should include HIV, human T cell lymphotropic virus, hepatitis B and C, toxoplasmosis, cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex virus (HSV) and varicella zoster virus.

Tuberculosis screening: There is an increased risk for tuberculosis (TB) following organ transplantation, with an increased risk for dissemination compared with the general population (67,68). Management of TB post-transplant is also associated with significant morbidity and mortality (69). For all of these reasons, transplant candidates should undergo TB screening with a tuberculin skin test and risk factor assessment before transplantation. Following screening to rule out active TB, those at risk for reactivation of latent TB following transplant based on either a positive tuberculin skin test or risk factor assessment should receive treatment for latent TB infection with isoniazid under the supervision of a physician with experience in TB management.

Immunization: Immunization against vaccine-preventable diseases should ideally be completed before transplantation. *The Canadian Immunization Guide* (70) and provincial immunization guidelines should be followed, with infectious diseases consultation as needed. In addition to routine vaccinations, all transplant candidates should receive a pneumococcal vaccine, a yearly influenza vaccine and a hepatitis B vaccine. Hepatitis B vaccination, with a documented serological response, allows for the safe use of hepatitis B core antibody-positive donors, thus expanding the donor pool (71). Susceptible individuals should receive varicella vaccine (live vaccine) a minimum of four weeks before transplantation.

CMV: CMV remains a significant cause of morbidity in organ transplant recipients; however, strategies for prevention have decreased the morbidity and mortality from CMV. The risk of CMV disease depends on a number of factors including the donor and recipient serostatus as well as the specific regimen of immunosuppression used. The Canadian Society of Transplantation consensus on CMV management in solid organ transplantation (72) should be used to guide institutional approaches to CMV prevention.

EBV: Primary EBV infection after transplantation has been identified as the most important risk factor for post-transplant lymphoproliferative disorder (PTLD), a complication with mortality reported in up to 40% to 60% of infections. This risk is exacerbated by the occurrence of CMV disease and treatment with polyclonal or monoclonal antilymphocyte antibodies. Studies comparing transplant recipients receiving antiviral prophylaxis with either acyclovir or ganciclovir to historical controls, suggest some benefit from antiviral prophylaxis (73). Recently, quantitative EBV viral load monitoring has also been shown to decrease the risk of PTLD (74).

Hepatitis B virus: Transplant candidates who are hepatitis B surface antigen-positive should be referred to a physician with expertise in the management of the hepatitis B virus. Those who meet indications for treatment before transplantation should be initiated on therapy. Those with e antigen-negative inactive hepatitis B virus before transplantation are at high risk for e antigen reactivation following transplant and should be placed on a nucleoside analogue (eg, lamivudine) at the time of transplantation. Because the risk of reactivation persists throughout the post-transplant period, this should be continued for the rest of the patient's life.

HSV: In the absence of prophylaxis, 24% to 34% of transplant recipients will have HSV disease. Antiviral prophylaxis in HSV-seropositive recipients should be considered for the first 30 days post-transplant to prevent HSV reactivation.

Pretransplant infections of VADs: VADs are increasingly used as a bridge to transplantation. Infections of such devices occur in 25% to 70% of cases, depending to a large extent on the duration of support. Although VAD infection has been associated with increased pretransplant mortality, no difference in post-transplant survival has been observed (75-78).

PTLD

PTLD is strongly associated with EBV and represents a highly diverse spectrum of disease with variable clinical presentation, from benign B cell proliferation (mononucleosis) to true monoclonal malignancy. PTLD may be nodal or extranodal, localized or disseminated and commonly involves the allograft. The diagnosis of PTLD requires histological confirmation and staging of the disease (79).

Options for the treatment of PTLD depend on the histology and stage of the disease; however, in all cases, attempts should be made to reduce or withdraw immunosuppression. Additional considerations for treatment will depend on the clinical presentation, histology and stage of disease. A multidisciplinary approach to management is generally indicated with collaboration between the transplant physician and the hematology, oncology, infectious disease and surgery departments depending on the clinical setting. In addition to immunosuppression reduction or withdrawal, potential options for therapy include antiviral agents, IV Ig, surgical resection and local radiation. Anti-CD20 monoclonal antibody (rituximab) therapy is an attractive second-line option if reduction in immunosuppression alone fails because of its low toxicity and favourable response rates (61% to 76%) (80). Cytotoxic chemotherapy is generally considered a third-line option due to a high incidence of toxicity in this population. Interferon-alfa has been used, but it often precipitates rejection.

Other malignancies

Skin and solid organ malignancies remain an important cause of mortality and morbidity following cardiac transplantation. Non-PTLD malignancy prevalence in cardiac transplant recipients is 13.6% and 29.8% at five and 10 years post-transplant, respectively (38). Skin malignancies remain the most common post-transplant malignancies, occurring in 20% of 10-year transplant survivors (38). Malignancies account for 23% of deaths after five years post-transplant, making this the second leading cause of death after allograft vasculopathy (38). Screening for malignancy should be performed in post-transplant patients as part of their routine follow-up.

ACAD

While the incidence of ACAD has decreased since the 1990s, it remains a major cause of morbidity and mortality after cardiac transplantation, accounting for 18% and 33% of deaths after five and 10 years, respectively (38). By 10 years post-transplant, ACAD is present angiographically in more than 50% of survivors (38). Early ACAD, defined as disease present within one year of transplantation, is associated with a significant increase in the five-year mortality rate, and likely represents a more aggressive form of allograft vasculopathy.

Immunological factors, as well as traditional coronary risk factors, likely play a role in the pathogenesis of ACAD (81). Transplant-specific risk factors for the development of ACAD include older donor age (particularly male donors) and pretransplant CAD or diabetes in the recipient (38). Screening and diagnosis of ACAD was reviewed in detail in the previous consensus document (1) and the recommendations remain valid.

Prevention of ACAD includes the reduction of traditional risk factors for CAD. Statin therapy has been associated with a reduction in ACAD (82,83). Some data suggest that a tacrolimus-based immunosuppressive regimen is associated with less coronary intimal thickening than with a cyclosporine-based regimen (84). Newer immunosuppressive agents, including sirolimus and everolimus (85-89), have shown some early promise in reducing intimal thickening, but their routine use for this purpose requires additional study.

Currently, there are no consistently effective treatments for established ACAD. Some studies have suggested that aggressive immunosuppression may be beneficial in the management of ACAD. High doses of steroids and ATG were associated with reduced progression and, in some cases, regression of ACAD in one small study (90), but the risks, including increased infection and malignancy, likely outweigh the benefits of this approach. Attenuation of the progression of ACAD has been seen in patients with established ACAD in whom sirolimus was added to CNI therapy (91). Similar results were seen in another study (92) in which rapamycin was used to replace CNI therapy; however, the incidence of rejection in the absence of CNI increased significantly. Based on these findings, many centres consider adding rapamycin in patients with documented ACAD. It is not clear whether CNI can or should be discontinued in these patients due to the increased risk of rejection, or whether patients with a longer period of time following transplantation would have a smaller risk of infection and be more likely to tolerate discontinuation of CNI therapy. Percutaneous coronary intervention using coronary stents has been more successful than balloon angioplasty alone (93); however, even in the setting of a successful procedure, the prognosis of patients with advanced ACAD remains poor.

MECHANICAL CIRCULATORY SUPPORT

The use of VADs as bridges to transplantation is now common, with many centres reporting pretransplant VAD support in as many as 50% of patients undergoing transplantation (94). Similar rates of VAD use are occurring in many Canadian transplant centres (unpublished results). With increasing experience in the management of patients with VAD support and improved VAD technology, complications have decreased, and survival to transplantation and beyond has increased.

CARDIAC RETRANSPLANTATION

Cardiac retransplantation is an uncommon procedure comprising approximately 2% of all adult heart transplants and 6% of pediatric heart transplants. Survival rates are significantly decreased compared with primary transplants. Patients who are younger, those who are retransplanted more than one year after the initial transplant, and those with either graft vasculopathy or chronic rejection as the reason for retransplantation have more reasonable outcomes. There is debate about the appropriateness of retransplantation but the final decision for suitability of retransplantation resides with the transplant physicians and the local review process (38,95,96).

SUMMARY

The Canadian Cardiovascular Society published its first Consensus Conference on cardiac transplantation in 2003 (1).

The present Executive Summary provides an update to the previous document with some modifications to listing criteria and indications, donor and recipient management, with special focus on the highly sensitized patients, induction, and an update on immunosuppressive therapy.

ENDORSEMENT: The present article is endorsed by the Canadian Society of Transplantation.

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