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Society Position Statement

Canadian Cardiovascular Society/Canadian Cardiac Transplant Network Position Statement on Heart Transplantation: Patient Eligibility, Selection, and Post-Transplantation Care

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ABSTRACT

Significant practice-changing developments have occurred in the care of heart transplantation candidates and recipients over the past decade. This Canadian Cardiovascular Society/Canadian Cardiac Transplant Network Position Statement provides evidence-based, expert panel recommendations with values and preferences, and practical tips on: (1) patient selection criteria; (2) selected patient populations; and (3) post transplantation surveillance. The recom-

RÉSUMÉ

Les pratiques relatives aux soins prodigués aux candidats à une transplantation cardiaque et aux receveurs d'un nouveau cœur ont beaucoup évolué depuis dix ans. Le présent énoncé de position conjoint de la Société canadienne de cardiologie et du *Canadian Cardiac Transplant Network* fait état des recommandations d'un groupe d'experts fondées sur des données probantes, et comprend des valeurs et des préférences ainsi que des conseils pratiques concernant

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This statement was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian panel comprised of multidisciplinary experts on this topic with a mandate to formulate disease-specific recommendations. These recommendations are aimed to provide a reasonable and practical approach to care for specialists and allied health professionals obliged with the duty of bestowing optimal care to patients and families, and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. The statement is not intended to be a substitute for physicians using their individual judgement in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

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mendations were developed through systematic review of the literature and using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system. The evolving areas of importance addressed include transplant recipient age, frailty assessment, pulmonary hypertension evaluation, cannabis use, combined heart and other solid organ transplantation, adult congenital heart disease, cardiac amyloidosis, high sensitization, and post-transplantation management of antibodies to human leukocyte antigen, rejection, cardiac allograft vasculopathy, and long-term noncardiac care. Attention is also given to Canadian-specific management strategies including the prioritization of highly sensitized transplant candidates (status 4S) and heart organ allocation algorithms. The focus topics in this position statement highlight the increased complexity of patients who undergo evaluation for heart transplantation as well as improved patient selection, and advances in post-transplantation management and surveillance that have led to better long-term outcomes for heart transplant recipients.

les critères de sélection des patients, des populations de patients particulières et la surveillance post-transplantation. Ces recommandations ont été formulées à la suite d'une revue exhaustive de la littérature et au moyen du système GRADE (*Grading of Recommendations Assessment, Development, and Evaluation*). Les domaines d'importance en évolution abordés comprennent l'âge du receveur, l'évaluation de sa fragilité, l'évaluation de l'hypertension pulmonaire, l'usage de cannabis, la transplantation cardiaque jumelée à la greffe d'un autre organe solide, la cardiopathie congénitale chez l'adulte, l'amylose cardiaque, la sensibilisation élevée ainsi que la prise en charge des anticorps à l'antigène leucocytaire humain, du rejet du greffon, de l'artériosclérose accélérée du greffon cardiaque et des soins non cardiaques de longue durée après la transplantation. Il est aussi question des stratégies de prise en charge propres au Canada, notamment l'établissement de la priorité des candidats à la transplantation hautement sensibilisés (statut 4S) et les algorithmes d'attribution des organes. Les thèmes principaux de cet énoncé de position font ressortir la complexité croissante des cas des patients qui subissent une évaluation en vue d'une transplantation cardiaque ainsi que l'amélioration des critères de sélection des patients et les avancées dans la prise en charge et la surveillance après la transplantation, qui permettent aux receveurs d'une greffe cardiaque d'obtenir de meilleurs résultats à long terme.

The Canadian Cardiovascular Society published the first heart transplantation (HTx) guidelines in 2003, and a last update in 2009.[1,2] Over the past decade, there have been significant practice-changing developments in patient evaluation and post transplantation care.[3] The objective of this position statement is to provide a focused update, review, and recommendations to assist clinicians and health care workers managing HTx patients in 3 areas: (1) patient selection criteria; (2) selected patient populations; (3) post transplantation surveillance and management. The systematic review approach, and methods for formulating the recommendations, values and preferences, and practical tips are detailed on the Canadian Cardiovascular Society Web site (www.ccs.ca). The recommendations use the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system,[4] which classifies the quality of evidence as high (further research very unlikely to change confidence in the estimate of effect), moderate (further research likely to have an important effect on confidence in the estimate of effect and might change the estimate), low (further research very likely to have an important effect on confidence in the estimate of effect and likely to change the estimate), and very low (estimate of the effect very uncertain). This system provides 2 grades of recommendations: "strong" (desirable effects clearly outweigh undesirable effects or clearly do not) and "weak" (trade-offs are less certain, either because of low-quality evidence or because the evidence suggests desirable and undesirable effects are closely balanced).

Selection Criteria

Age

The median HTx recipient age has increased from 53 to 55 years over the past decade.[5,6] Although increased age is associated with post transplantation mortality, HTx in septuagenarians is becoming more frequent.[5-7] Large registry analyses have shown similar post transplantation survival and morbidity in patients $\geq$ 70 years of age compared with younger patients, suggesting acceptable outcomes can be achieved through careful selection.[8,9]

RECOMMENDATION

1. We recommend consideration of HTx for eligible patients with advanced heart failure (HF) who are $\leq$ 70 years of age (Strong Recommendation, Low-Quality Evidence).
2. We suggest HTx might be considered for carefully selected patients with advanced HF > 70 years of age (Weak Recommendation, Low-Quality Evidence).

Frailty

Frailty in patients with advanced HF is associated with increased morbidity and mortality with an approximate 25% reduction in 1-year post-HTx survival in frail patients.[10] The presence of cachexia, self-reported physical exhaustion or decrease in hand grip strength, walking speed, or physical activity[11] have been used to define frailty.[9] Several tools for assessing frailty have been used for patients who undergo HTx and left ventricular assist device (LVAD) placement including the Fried Frailty Phenotype score ($\geq$ 3 of 5 measures), the Deficit Index ($\geq$ 0.32), and the Edmonton Frailty Scale score ($\geq$ 8; Table 1).[10] Additionally, reduced preoperative muscle mass significantly increases postoperative morbidity and mortality. The prognostic value of a frailty assessment might be increased by including cognitive and depression measures such as a Montreal Cognitive Assessment score $\leq$ 26 and Depression in the Medically Ill-10 score $\geq$ 9, respectively.[12]

Table 1. Frailty assessment tools

Model	Domain	Assessment	Calculation
Fried Frailty Phenotype	Grip strength	Handheld dynamometer (in kilograms) and stratified according to gender and body mass index quartiles; 1 point	All values are summed with ≥ 3 consistent with frailty in HF patients
	Walk time	Time to walk 15 feet stratified according to gender and height; 1 point	
	Low level of physical activity	"How often do you engage in activities that require a low or moderate level of energy, such as walking, chores (moderately strenuous), mowing the lawn, raking, gardening, hiking, jogging, exercise cycling, dancing, aerobics, bowling, golf, tennis, racquetball, calisthenics, swimming." Kcals per week expended are calculated using standardized algorithm Men: Kcals per week < 383 are frail; 1 point Women: Kcals per week < 270 are frail; 1 point	
	Exhaustion	The following 2 statements are read: "I felt that everything I did was an effort?" and "I could not get going?" "How often in the week did you feel that way?" (0 = rarely or none of the time (1 day), 1 = some or a little of the time (1-2 days), 2 = moderate amount of the time (3-4 days), 3 = most of the time. A response of "2" or "3" to either question is considered as exhaustion and categorized as frail; 1 point	
	Weight loss	"In the past year, have you lost more than 10 pounds unintentionally (ie, not due to dieting or exercise)?" If yes, then frail for weight loss criterion; 1 point	
Deficit Index	Mobility	Walking speed; number of falls in the past 6 months	Points assigned using standard methods of assessments and divided by the total number of domains assessed. Value ≥ 0.32 considered significant for HF patients
	Cognition	History of dementia; Mini-Cog test or Mini-Mental State Examination	
	Exhaustion	Dependency of activities in daily living	
	Function	Energy level	
	Burden of chronic disease	Charlson index; > 5 chronic medications	
	Mood	Depression, sadness, anxiety	
	Nutritional status	> 10-Pound weight loss in the past 6 months; low albumin, poor appetite	
	Social vulnerability	Presence of social support; lack of interactions with other people	
Edmonton Frailty Scale	Cognition	Please imagine that this predrawn circle is a clock. I would like you to place the numbers in the correct positions then place the hands to indicate a time of "ten after eleven"; 0 points = no errors, 1 point = minor spacing errors, 2 points = other errors	Points are tallied with score ≥ 8 of 17 considered significant for frailty in HF patients
	General health status	In the past year, how many times have you been admitted to a hospital? 0 points = 0, 1 point = 1-2, 2 points ≥ 2. In general, how would you describe your health? 0 points = excellent, very good, good; 1 point = fair; 2 points = poor	
	Functional independence	With how many of the following activities do you require help? (meal preparation, shopping, transportation, telephone, housekeeping, laundry, managing money, taking medications); 0 points = 0-1, 1 point = 2-4, 2 points = 5-8	
	Social support	When you need help, can you count on someone who is willing and able to meet your needs? 0 points = always, 1 point = sometimes, 2 points = never	
	Medication use	Do you use 5 or more different prescription medications on a regular basis? 0 points = no, 1 point = yes. At times, do you forget to take your prescription medications? 0 points = no, 1 point = yes	
	Nutrition	Have you recently lost weight such that your clothing has become looser? 0 points = no, 1 point = yes	
	Mood	Do you often feel sad or depressed? 0 points = no, 1 point = yes	
	Continence	Do you have a problem with losing control of urine when you don't want to? 0 points = no, 1 point = yes	
	Functional performance	I would like you to sit in this chair with your back and arms resting. Then, when I say "Go," please stand up and walk at a safe and comfortable pace to the mark on the floor (approximately 3 m away), return to the chair and sit down. 0 points = 0-10 seconds, 1 point = 11-20 seconds, 2 points = > 20 seconds, unwilling, or unable	

HF, heart failure.
Modified from Mauthner et al.[14] with permission from Elsevier; and Rolfson et al.[15] with permission from Oxford University Press.

Prehabilitation has been shown to be beneficial in patients who receive cardiac surgery, but these studies have not included pre-HTx patients. LVADs can be implanted as a bridge to transplantation strategy and might promote an anabolic state thereby decreasing frailty while awaiting transplantation.[13] However, there are conflicting data and

uncertainty over the benefit of LVADs to reverse frailty in advanced HF patients.[14]

RECOMMENDATION

3. We recommend an assessment of frailty using the Fried Frailty Phenotype score, Deficit Index, or Edmonton Frailty Scale, for example, for all patients being considered for HTx (Strong Recommendation, Moderate-Quality Evidence).

Values and preferences. LVAD placement in selected patients might be considered to improve frailty before HTx.

Obesity

Elevated body mass index (BMI) is an important predictor of poor survival after HTx.[6] High BMI is also associated with up to 46% lower likelihood of finding a suitable donor and prolonged waiting time to HTx.[16] Observational studies have shown that BMI $\geq$ 35 is associated with decreased patient survival post HTx and increased risk of infection, rejection, diabetes, and cardiac allograft vasculopathy (CAV).[9,16-18] Increased adverse outcomes after HTx have not been consistently shown for obese patients with BMI 30-34.9 compared to patients with BMI $<$ 30. In selected obese patients, LVAD implantation as a bridge to transplantation achieves reasonable outcomes. A BMI $\geq$ 35 is associated with increased risk of complications such as thromboembolism and infection but no difference in survival post LVAD implantation.[19] Weight loss can be achieved but is uncommon post LVAD placement, and additional weight loss strategies are generally recommended before transplant listing.

RECOMMENDATION

4. We recommend caution in HTx for patients with a BMI $\geq$ 35 (Strong Recommendation, Low-Quality Evidence).

Pulmonary hypertension

Significant pulmonary hypertension (PH), typically defined as pulmonary vascular resistance $>$ 3 Wood Units, transpulmonary gradient $>$ 15 mm Hg and/or pulmonary artery systolic pressure $>$ 50 mm Hg, is considered a contraindication for HTx[9] because of greater risk of post-transplantation right ventricular failure and early mortality.[20,21] All patients being evaluated for HTx should undergo right heart catheterization to evaluate pulmonary hemodynamics. An acute vasodilator challenge is recommended in patients with PH to assess for reversibility, which is defined as achieving all the following: pulmonary vascular resistance $<$ 3 Wood Units, transpulmonary gradient $\leq$ 14, pulmonary artery systolic pressure $<$ 50 mm Hg while maintaining a systolic blood pressure $>$ 85 mm Hg. If unsuccessful, further medical optimization with inotropes, diuretics, and vasoactive therapies should be considered. Inhaled (eg, nitric oxide) or intravenous (eg, sodium nitroprusside, nitroglycerin) agents can be used for the vasodilator challenge; systemic effects such as hypotension are greater with intravenous compounds.[9] Concomitant conditions that can exacerbate PH such as chronic obstructive pulmonary disease, sleep apnea, and pulmonary emboli should be aggressively treated.[22] If medical therapy fails to achieve acceptable pulmonary hemodynamics and primary pulmonary causes of PH have been excluded, an LVAD should be considered to maximize left ventricular unloading and pulmonary vascular remodelling.[23] Most studies have shown significant reduction in pulmonary pressures post LVAD placement.[23,24] Hemodynamic reevaluation is performed at 3-6 months after LVAD placement to ascertain PH reversibility. A small number of single-centre studies have successfully used phosphodiesterase-5 inhibitors to reduce PH and facilitate candidacy for HTx without LVAD placement.[25-27] Their use needs to be balanced against the risks of systemic hypotension and worsening pulmonary edema, and are currently not routinely recommended in patients being considered for HTx. In the small subset of patients who have persistent PH after LVAD implantation, phosphodiesterase-5 inhibitors can be considered as adjunctive therapy.[28]

RECOMMENDATION

5. We recommend right heart catheterization for assessment of PH, PH severity, and reversibility in all patients being evaluated for HTx (Strong Recommendation, Low-Quality Evidence).
6. We recommend an acute vasodilator challenge for patients with evidence of PH on right heart catheterization (Strong Recommendation, Low-Quality Evidence).
7. We recommend LVAD implantation for eligible patients with significant PH who are otherwise candidates for HTx (Strong Recommendation, Moderate-Quality Evidence).
8. We recommend against routine use of phosphodiesterase-5 inhibitors to reduce pulmonary pressures in patients with advanced HF and PH (Weak Recommendation, Moderate-Quality Evidence).

Psychosocial considerations and substance use

The International Society of Heart and Lung Transplantation (ISHLT) recently published a consensus statement on pre-HTx psychosocial evaluation.[29] Contraindications to HTx included: repeated medical nonadherence, active alcohol

or drug abuse, active smoking, and mental health and social conditions that are likely to affect ability to adhere to medication regimens.[29] Psychosocial problems might be remediated and also inform care planning post HTx. However, there is minimal literature documenting the effect of interventions on HTx outcomes.

RECOMMENDATION

9. We recommend psychosocial evaluation before HTx (Strong Recommendation, Low-Quality Evidence).
10. We recommend attempts to remediate modifiable psychosocial factors in candidates for whom these are barriers to transplant listing (Strong Recommendation, Very Low-Quality Evidence).
11. We do not recommend HTx for patients who show repeated nonadherence to medications, alcohol use disorder, smoking or illicit drug use, mental illness or other cognitive factors, and/or insufficient social support, which are likely to affect ability to adhere to medication and post-transplantation regimens (Strong Recommendation, Low-Quality Evidence).

Practical tip. To optimize post-HTx outcomes, the psychosocial assessment should attempt to answer the following 3 questions: will the patient take medications as ordered, attend clinic appointments, and call if there is a problem.

Cannabis. Cannabis refers to cannabis, its by-products, and synthetic cannabinoids. On October 17, 2018, the Federal Government of Canada passed Bill C-45—the Cannabis Act, which changed cannabis use from "illicit" drug use to an accepted recreational activity.[30]

In a recent systematic review, cannabis use was shown to increase heart rate and reduce blood pressure, but there was insufficient evidence to determine whether cannabis was responsible for arrhythmia, ischemia, and sudden death.[31] The potential for pulmonary infections from smoking cannabis is described in case reports of immunosuppressed patients possibly because of inhalation of fungal elements.[32] These reports are published in an era of illicit use and presumably nonregulated production. Other risks associated with smoking or vaping cannabis are unknown. Until evidence to the contrary emerges, smoking or vaping cannabis should be actively discouraged. Cannabis and immunosuppression drug interactions has not been well studied. A systematic review of 31 studies on whether cannabinoids could affect human drug-metabolizing enzymes (including cytochrome P-450) concluded insufficient evidence to confirm any interactions in humans. Moreover, it was difficult to determine the exact effects because of variable cannabis usage.[33] One small study of 6 HTx cannabis users showed that calcineurin inhibitors (CNIs) cyclosporine and tacrolimus dose to trough ratio was reduced by 21% and 3%, respectively. There was no difference in outcomes compared with other HTx patients.[34]

RECOMMENDATION

12. We recommend 6 months abstinence from smoking, inhaling, or vaping cannabis before HTx listing (Strong Recommendation, Low-Quality Evidence).

Values and preferences. Recreational or medicinal noninhalational cannabis use is not an absolute contraindication for HTx. Cannabis use disorder is a contraindication to transplantation and specialist treatment programs are warranted. Transplantation may be reconsidered upon completion and successful abstinence for a minimum of 6 months. We suggest additional monitoring of CNI levels in HTx recipients using cannabis.

Selected Patient Populations

Cardiac amyloidosis

Cardiac amyloidosis is a systemic disease caused by extracellular cardiac deposition of light chain (AL) or transthyretin (ATTR) protein fibrils.[35] Transplantation for advanced AL cardiac amyloidosis is controversial because of high wait list mortality of up to 40%[36] and inferior post transplantation survival compared with nonamyloid patients.[35] Historically, isolated HTx for AL cardiac amyloidosis was associated with a dismal 1-year survival of 50% because of recurrence of amyloid in the allograft or progression of extracardiac amyloid disease. Recent advances in bortezomib-based chemotherapy strategies for AL amyloidosis and improved patient selection for HTx have led to better outcomes. Single-centre series using a staged approach of HTx followed by autologous bone marrow stem cell transplantation 6-12 months later have increased 1- and 5-year survival rates to 82%-100% and 65%, respectively.[36-39] An analysis of the United Network for Organ Sharing database showed decreased post-transplantation mortality (hazard ratio, 0.49; $P = 0.03$) for patients with cardiac amyloidosis in 2008-2013 compared with an earlier 1987-2007 era.[40] Recent studies of patients who received a heart transplantation within the past 5 years have shown an even smaller gap in outcomes between amyloid and nonamyloid patients with 90% survival at 1 year in one case series.[39] Importantly, a detailed evaluative process is crucial to assess for multiorgan involvement that might preclude HTx.[9,41] A multidisciplinary management approach is required involving specialists from hematology, neurology, nephrology, and gastroenterology.

Transthyretin amyloidosis might occur as hereditary ATTR (hATTR) or wild type ATTR (ATTRwt) forms. Liver or combined heart-liver transplantation (HLivT) are treatment options aimed at removing hepatic production of the mutant protein. Disease progression for ATTRwt is generally slower than for hATTR and ATTRwt is predominantly a disease of the elderly, who usually have comorbidities precluding HTx.[42] Emerging medical treatments for ATTR amyloid have shown potential to significantly reduce progression of cardiac disease.[43]

RECOMMENDATION

13. We suggest consideration of HTx in highly selected patients with isolated cardiac amyloidosis together with treatment to suppress the amyloidogenic process (Weak Recommendation, Low-Quality Evidence).

Values and preferences. HTx is feasible for highly selected patients with cardiac amyloidosis and non-advanced systemic disease. In conjunction with contemporary chemotherapy regimens, outcomes post HTx for AL cardiac amyloidosis are comparable with nonamyloid cardiomyopathy. Patients should be managed by a multidisciplinary team involving expertise in solid organ and bone marrow transplantation.

Practical tip. Patients with isolated AL cardiac amyloidosis requiring HTx should be treated with chemotherapy and show appropriate reduction in light chains, followed by HTx and autologous bone marrow transplantation if eligible. For patients with hATTR amyloidosis, combined heart and liver transplantation may be considered. The long-term effects of the newer therapies targeting ATTR need to be evaluated.

Retransplantation

Cardiac retransplantation comprised 6% of HTx reported to the ISHLT in 2017.[6] Although retransplantation is often the only effective long-term treatment option for patients with allograft dysfunction, inferior outcomes compared with *de novo* HTx have been reported in multiple large registry analyses, and questioning appropriateness of retransplantation, particularly because of the shortage of donor organs.[44-46] In a recent meta-analysis of 11 studies including 7446 patients with primary HTx and 345 with retransplantation (mean of 5 years post primary HTx, 35% retransplantation within 30 days of primary HTx), actuarial survival was significantly greater among primary HTx patients: 82% vs 59% at 1 year, 67% vs 41% at 5 years, 54% vs 32% at 10 years for primary and retransplantation, respectively.[47] The mortality differences were largely because of greater early mortality of 28% for retransplantation compared with 11% for *de novo* HTx. Data from the joint ISHLT/United Network for Organ Sharing registries suggested that poor outcomes after retransplantation was associated with shorter time between transplantations, with an interval of < 2 years resulting in < 60% 2-year survival. Furthermore, data from the Cardiac Transplant Research Database showed that survival was lowest among patients who received retransplantation for acute rejection (AR; 32% at 1 year) and early graft failure (50% at 1 year).[44]

RECOMMENDATION

14. We recommend cardiac retransplantation for highly selected patients with severe chronic allograft dysfunction (Strong Recommendation, Moderate-Quality Evidence).

Values and preferences. Retransplantation should be avoided in patients with AR.

Adult congenital heart disease

There are no published evidence-based or consensus guidelines regarding adult congenital heart disease (ACHD) patients and HTx. Prognostication is difficult because most of the data are derived from retrospective single-centre[48-59] or registry-based studies[60-70] with no randomized trials and only 1 meta-analysis published to date.[71] Timing of referral for HTx assessment is difficult because of the lack of robust data correlating any specific factors with outcomes. Thus, the general practice is to consider transplantation for progressive symptoms when alternate management options are no longer effective and/or beneficial.

RECOMMENDATION

15. We recommend early referral for assessment of HTx in patients with ACHD with progressive cardiac symptoms despite optimal medical, surgical, and interventional therapies (Strong Recommendation, Very Low-Quality Evidence).

Practical tip. ACHD patients should be referred early and followed by transplant and ACHD teams to determine optimal timing for transplant listing. HTx should be considered as a potential management strategy in ACHD patients even when some surgical options might be available.

Anatomic substrate, including systemic right vs left ventricle and single vs biventricular heart has been associated with pretransplantation outcomes.[59,65] Brain natriuretic peptide (BNP) has been studied but normal and prognostically significant values in ACHD patients with different anatomical considerations are not well defined.[52,58] Serial cardiopulmonary exercise testing might have predictive value, but no thresholds predicting mortality have been defined.[53,54] Response to cardiac resynchronization therapy,[55] PH and reversibility,[67] and liver disease[48] have all been reported to impact pre- and post-HTx outcomes but currently available data do not provide information about survival with or without transplantation, and/or guide listing or listing status decisions.

The pretransplantation assessment must consider all factors relevant to a noncongenital patient but also requires input from specialized practitioners on factors unique to this patient population including: sensitization (higher prevalence), PH (different mechanisms requiring expertise to assess), complex anatomy with potential need for nonstandard anastomoses, previous surgeries (eg, reentry risk, vascular access, collaterals), liver disease (eg, cirrhosis, portal hypertension, varices), and Fontan physiology (eg, protein-losing enteropathy, plastic bronchitis, ascites and edema, cyanosis, lymphatic drainage abnormalities, pulmonary arteriovenous malformations). The decision regarding transplant candidacy is on the basis of the cumulative sum of multiple relative risk factors. The complexity of the decision-making, the lack of evidence, and the small, very diverse patient population warrant management at a centre with expertise in ACHD, transplantation, and mechanical circulatory support.

RECOMMENDATION

16. We recommend patients with ACHD undergo evaluation and HTx at centres with multidisciplinary expertise in congenital heart disease and transplantation (Strong Recommendation, Low-Quality Evidence).

Values and preferences. Factors unique to patients with ACHD must be considered during HTx assessment.

ACHD patients are disadvantaged in current organ allocation algorithms.[71,72] They are listed at a lower status,[62,63,66] less likely to reach criteria for higher status,[62,63,66] wait longer at any given status,[61,62,69] have a higher wait list mortality,[64] and are less likely to get a transplant.[62,69] They are disadvantaged by the higher priority given to non-ACHD patients supported with a ventricular assist device,[63,72] and lower likelihood of being successfully supported with a ventricular assist device.[63,72] As such, review and revision of listing algorithms and allocation should be undertaken.

Ischemic time has been shown to be a risk factor for early mortality in ACHD transplant recipients.[49,50] Increasing ischemic time is associated with reduced survival, and the probability of death is further increased in the older recipient with an older donor and longer ischemic time.[69] ACHD transplant recipients have increased perioperative and early post-transplantation mortality,[60,61,66,69-71] due to hemorrhage, renal failure, multisystem organ failure, and primary graft failure.[70,71] However, they have better long-term survival and outcomes because of younger age, fewer comorbidities, and reduced risk for infection.[49,50,60,61,69-71]

RECOMMENDATION

17. We recommend particular attention be paid to the effect of older donor age and/or longer ischemic time on survival outcomes when considering a donor organ for a patient with ACHD (Strong Recommendation, Moderate-Quality Evidence).

Values and preferences. Because of the high early postoperative mortality but better long-term outcomes in ACHD transplant recipients, there is a need to better define indications and timing of listing, as well as pre-, peri-, and postoperative care needs to reduce perioperative mortality.

Combined solid organ transplantation

Combined organ transplantation volumes have increased over the past several years, but continue to represent a very small proportion of overall HTx. In the 2016 ISHLT registry, heart-kidney transplantation (HKT) and HLivT accounted for approximately 4% of all HTxs, and heart-lung transplantation (HLungT) accounted for < 2% of all lung transplants performed.[6,73] Because of the relatively small numbers, data on combined heart-other organ transplantation are primarily derived from single centres and large registries. Despite these limitations, common themes have emerged, namely a more complex perioperative course with longer critical care and hospital length of stays post combined organ transplantation.[6] Strikingly, 1-year waitlist mortality is approximately 2-fold higher than for isolated HTx candidates.[74,75] This suggests combined organ transplantation candidates are disadvantaged in the current organ allocation system, and a need to revise allocation schemes and consider prioritizing access to donor organs.

HKT. Most available data regarding HKT reflects simultaneous rather than sequential "kidney after heart" transplantation. Approximately half of all patients who undergo HKT are dialysis-dependent while listed.[74] In this context, large registries of > 1300 HKT candidates suggests that HKT confers a survival benefit over isolated HTx among patients who are dialysis-dependent or who have very low glomerular filtration rate (typically < 30-40 mL/min/1.73 m^2) at the time of transplantation.[74,76] Recent ISHLT registry data confirm modestly improved survival for HKT patients and similar incidence of long-term comorbidities compared with heart-alone transplant patients.[6]

RECOMMENDATION

18. We recommend combined HKT (simultaneous or sequential) be considered to improve survival in HTx candidates with severe renal failure for whom the probability of renal recovery is very low (Strong Recommendation, Moderate-Quality Evidence).

Values and preferences. The decision to list patients for simultaneous HKT vs planned sequential heart followed by kidney transplantation should be individualized and consider several factors, including dialysis dependency before transplantation, centre experience, potential for further recipient sensitization, and anticipated waitlist mortality. There are no universally accepted criteria for listing patients for combined HKT.

HLivT. The common indications for HLivT are advanced HF with cardiac cirrhosis, HF with concomitant noncardiac cirrhosis, or advanced HF with associated liver disease in which the liver is transplanted to avoid ongoing damage to the cardiac allograft. Amyloidosis is the prototypical example of the latter, and remains the most common indication, accounting for 25%-30% of combined HLivT.[77] A consistent observation is that the Model for End-Stage Liver Disease score, which is used to assess severity of liver disease, is generally lower in HLivT than for patients listed for liver alone, and in most cases, cardiac dysfunction is the primary driver of combined organ transplant.[77]

Data from the United Network for Organ Sharing including nearly 100 HLivT demonstrate excellent liver and cardiac allograft survival and similar to isolated liver or HTx.[77] These findings have been corroborated by a number of single-centre reports and a consistent signal toward reduced incidence of cardiac allograft rejection in patients with HLivT has also been observed.[78] Of note, the subgroup of patients with ACHD who undergo HLivT has similar outcomes compared with non-ACHD patients.[78] It should be emphasized that observational

studies to date have reported on highly selected patients. At present, criteria and candidacy for HLivT are not standardized.

RECOMMENDATION

19. We suggest combined HLivT be undertaken in highly selected patients with advanced HF who have cardiac or noncardiac cirrhosis or systemic disease for whom simultaneous liver transplantation would be expected to improve cardiac allograft outcomes (Weak Recommendation, Moderate-Quality Evidence).

Fontan-associated liver disease in patients with Fontan circulation is an emerging indication for HLivT. Experience is limited to single centres and small numbers of registry patients. In highly selected patients, outcomes are generally excellent and might be superior to isolated HTx in Fontan patients whose mortality exceeds 15%-25% in some series.[79]

RECOMMENDATION

20. We recommend patients with failing Fontan circulation and severe Fontan-associated liver disease should be referred to experienced centres for evaluation for isolated heart or combined HLivT (Strong Recommendation, Very Low-Quality Evidence).

HLungT. The main indications for HLungT are Eisenmenger physiology or idiopathic pulmonary arterial hypertension with severe cardiac dysfunction. Median survival is approximately 5.8 years and similar to lung-alone transplantation,[73] however, this improves to 11.5 years among patients who survive beyond the first year after transplantation. Functional status post HLungT is generally excellent and greater freedom from cardiac rejection and CAV have been observed in this population. Bronchiolitis obliterans syndrome remains the leading cause of death in HLungT transplantation patients and occurs in approximately a third of patients 5 years post transplantation.[73]

RECOMMENDATION

21. We recommend patients being considered for simultaneous HLungT be referred to centres experienced in evaluation, surgical management, and postoperative care of HLungT recipients (Strong Recommendation, Low-Quality Evidence).

Values and preferences. This recommendation reflects the low number of HLungTs performed in Canada each year, and the need to balance high up-front perioperative risks with excellent long-term conditional survival.

Highly sensitized

The percentage calculated panel reactive antibody (cPRA) is an estimate of the proportion of organ donors with whom an HTx candidate might be incompatible on the basis of detectable antibodies against human leukocyte antigen (HLA) in the serum. Sensitization, measured according to elevated cPRA, is well recognized to be associated with adverse outcomes in HTx. Management strategies for a sensitized HTx candidate include desensitization, avoidance of donor-specific antibody (DSA) using virtual cross-matching, or a combination of the 2 approaches. In Canada, the current approach favours primarily avoiding DSA using the virtual cross-match and status 4S listing, whereby highly sensitized patients with cPRA > 80% have national access to organs and are second in priority only to highest urgency status 4 patients. The 4S status listing does not preclude desensitization therapy or mandate inclusion of all detected antibodies because of the complexity and variability in assessing antibody-specific immunologic risk. The status 4S system has shown effective expansion of the donor pool with satisfactory post-transplantation outcomes.[80] Revision of the 4S listing status category will yield a change to give ranking priority to the highest cPRA in descending fashion; cPRA 100% higher priority than 99%, followed by 98%, 90%-97%, and 80%-89% (Supplemental Tables S1 and S2).

RECOMMENDATION

22. We recommend using the cPRA calculator in the Canadian Transplant Registry for determination of cPRA (Strong Recommendation, High-Quality Evidence).

Practical tip. HLA antibody assessment and reporting are standardized across Canadian HLA laboratories. The Canadian cPRA calculator includes all loci including *DQA1*, *DPA1*, and *DPAB1* (https://ctr2.transplantregistry.ca/otd-cpra-client/ctr2.jsp).

RECOMMENDATION

23. We recommend collaborative consultation with the HLA laboratory to fully characterize immunologic risk of identified HLA antibodies in HTx candidates (Strong Recommendation, Moderate-Quality Evidence).

Values and preferences. Defining immunologic risk involves considerations beyond HLA antibody median fluorescence intensity. Collaborative consultation with histocompatibility laboratory specialists is recommended to determine the significance of the detected antibody and if further antibody characterization is warranted.

Desensitization therapies have evolved over the past 15 years (Table 2). However, the optimal strategy to improve immunologic and long-term outcomes remains unclear,

Table 2. Desensitization agents

Agent	Mechanism of action	Dosing	Complications
PLEX	Extracorporeal plasma antibody filtration • Temporary, redistribution from extravascular space, typically reserved for peri/post transplantation	1-2 volume exchange per cycle • Daily or every other day • Replace 5% albumin • Duration variable • Monitor fibrinogen; consider volume exchange with fresh frozen plasma	Access/line-related complications: bleeding, hypotension, allergic reactions; infection
IVIG	Pooled immunoglobulin G antibodies (human blood donors) Immunomodulatory effects: • Inhibition of complement deposition • T-cell FC receptor blockade • Suppression of cytokines and cytokine receptors • B-cell receptor downregulation	If given with PLEX: 0.1 g/kg after each cycle and 2g/kg over 2 days after the final cycle If given without PLEX: 2g/kg over 2 days every 2-4 weeks • Consider premedication with antihistamine/acetaminophen and slower infusion rates to reduce volume and side effects	Infusion reactions, hemolysis, venous thromboembolism, renal insufficiency, volume overload, hypertension
Rituximab	Monoclonal antibody with targeted B-cell CD20 inhibition • Often used in conjunction with other therapies (ie, IVIG, PLEX). CD20 is widely expressed from early pre-B to mature B cells, but not plasma cells • Can create false positive crossmatch (rituximab is partially human and activates complement)	1 g single dose or 375 mg/m^2 • Lymphocyte subsets 2 and 14 days post dose • Can be given before IVIG or 7, 14 days after first IVIG infusion • Target CD19 cell counts 0% • Consider additional dosing if CD19 > 3%	Infusion reactions, fever, hypotension, edema, nausea, anemia, myalgia
Bortezomib	Proteasome inhibitor; selectively depletes plasma cells • Consider if poor response to rituximab	1.3 mg/m^2	Neuropathy, thrombocytopenia, neutropenia
Eculizumab	Complement C5 inhibitor; monoclonal antibody binds C4 and prevents cleavage into C5a/b, preventing formation of membrane attack complex	• Minimal data for pretransplantation desensitization	Meningococcal infection

IVIG, intravenous immune globulin; PLEX, plasmapheresis.

because most studies have been of low quality with small patient numbers and with short follow-up.[81–83] Intravenous immune globulin (IVIG), targeted B cell (rituximab), and plasma cell therapies (bortezomib) form the foundation of desensitization treatments. Plasmapheresis and immunoadsorption treatments involve mechanical filtration of antibodies. Because of rebound effects, these can be effective in the short term, but adjunctive therapies are required for definitive control. There is limited experience with the complement inhibitor eculizumab.[84] Existing data on the efficacy of desensitization are primarily extrapolated from renal literature. Strategies involving IVIG and rituximab have increased transplantation rates, reduced wait list time, and reported graft outcomes similar to those of non-sensitized patients.[85-88] To our knowledge, there are no randomized trials on efficacy of desensitization therapy in HTx. Single-centre experiences in HTx have shown comparable short-term outcomes with varying combinations of IVIG, rituximab, bortezomib, plasmapheresis, and immunoadsorption compared with patients who receive a transplant with no DSA.[82,89-92] In addition, a strategy of intra and post-operative desensitization therapy involving plasmapheresis, IVIG and thymoglobulin (ATG) induction has been reported to have satisfactory short-term outcomes in highly sensitized HTx patients transplanted across DSA.[93]

RECOMMENDATION

24. We suggest consideration of desensitization therapies to facilitate transplantation and improve short-term transplantation-specific outcomes in highly sensitized populations such as patients with cPRA 50%-79% and previous positive virtual crossmatches; patients in urgent need of transplantation (status 4); and patients with very high cPRA listed status "S" (Weak Recommendation, Moderate-Quality Evidence).

Values and preferences. Most pretransplantation desensitization protocols include IVIG 2 g/kg divided over 2 days (and continued monthly) with the additional use of rituximab in either a single 375 mg/m^2 or 1 g dose. Effective B-cell depletion can be assessed by measuring lymphocyte cell subsets 2 days post administration with target CD19 < 2%. If there is no reduction in antibody after 3 months, alternative therapies such as bortezomib and eculizumab may be considered. Concurrent plasmapheresis may be reserved for short-term antibody depletion peri-, intra-, and postoperatively.

Practical tip. Desensitization decisions are made on an individual basis and should take into consideration patient- and

institution-specific factors. Patient-specific risks include infection, renal function and risk of deterioration, HF status, and personal preferences. Institution-specific factors include accessibility of organs, and historical wait times.

Organ Allocation

Please see the Supplemental Material for information on Canadian heart organ allocation (Supplemental Tables S1 and S2) and current matching and allocation policies for interprovincial sharing of high-status hearts (Supplemental Appendices S1-S5).

Post-Transplantation Management

Maintenance immunosuppression

Maintenance immunosuppression refers to the period following induction therapy post HTx. Most patients are maintained with a combination of 2-3 different class agents: CNIs, antimetabolites, corticosteroids, and proliferation signal inhibitors (PSIs). CNIs form the mainstay of immunotherapy. Several trials have evaluated CNI-free regimens, and have shown prevention of deterioration in renal function but at the cost of increased risk of rejection.[94,95] Importantly, improvement in renal function after conversion to a CNI-free regimen is less likely in patients with advanced chronic kidney disease.[94,96] Small randomized trials and 2 meta-analyses that compared CNI tacrolimus and cyclosporin showed lower rejection risk for tacrolimus and a more favourable side effect profile.[97] Tacrolimus is available in immediate and extended release formulations with the immediate release formulation best studied in HTx. The 2 formulations were compared in 2 small trials no significant differences in rejection, infection, or adverse events were observed.[98]

Mycophenolic acid is the preferred antimetabolite post HTx and has been shown to be superior to azathioprine. In one small randomized trial mycophenolate mofetil and enteric-coated mycophenolate-sodium were compared in HTx recipients and showed no difference in outcomes including rejection, graft loss, and death.[99]

RECOMMENDATION

25. We recommend a CNI and mycophenolic acid-based immunosuppression regimen after HTx for most patients (Strong Recommendation, Moderate-Quality Evidence).

Values and preferences. A CNI-free regimen is associated with increased risk of rejection, but might be justified in selected patients, particularly individuals with renal dysfunction.

26. We recommend tacrolimus over cyclosporin as the preferred CNI (Strong Recommendation, Low-Quality Evidence).

Values and preferences. Compared with cyclosporin, tacrolimus provides superior protection against rejection and has a more favourable side effect profile than cyclosporin.

The PSI sirolimus and everolimus have not been directly compared. Currently, everolimus is not approved in Canada for post-HTx immunosuppression. *De novo* treatment with PSI has been shown to reduce the development and progression of CAV and is associated with lower incidence of cytomegalovirus infection.[100-102] A PSI-based regimen can also facilitate CNI withdrawal to preserve renal function. Early post-transplantation PSI use has been associated with increased rejection in CNI-free regimens, pericardial effusions, wound healing problems, and infection. Similar survival and rejection rates have been observed in trials in which PSI and CNI have been compared vs CNI and mycophenolate mofetil. However, PSI has a lower tolerability profile with approximately twice as many patients needing to discontinue treatment because of adverse effects.

RECOMMENDATION

27. We recommend treatment with PSI to delay CAV progression and/or enable CNI withdrawal/minimization to preserve renal function in selected patients (Strong Recommendation, Moderate-Quality Evidence).

Values and preferences. Immunosuppression regimens should be individualized, balancing the risk of rejection, CAV, and cytomegalovirus infection with the adverse effects profile of each immunotherapy.

PSIs have intrinsic antitumour activity and have been successfully used as a therapy for cancer. Several studies in noncardiac solid organ transplantation have suggested a malignancy risk reduction in patients who receive PSIs.[103,104] The ongoing A Secondary Prevention Study of Skin Cancers in Heart Transplant Patients. Everolimus Versus Calcineurin Inhibitors Multicenter Trial (CERTICOEUR) trial (NCT00799188), in which everolimus is being compared with CNI in HTx recipients with skin cancer, is the only randomized trial examining cancer reduction with PSI use in the HTx population. Most published trials that have compared PSIs with other immunotherapy did not include malignancy as an outcome or had a short follow-up time. However, retrospective studies suggest a reduction in cutaneous and noncutaneous malignancies in patients treated with a PSI, with either reduced-dose CNIs or a CNI-free regimen.[103,105-107]

RECOMMENDATION

28. We suggest reducing maintenance immunotherapy and including a PSI in patients diagnosed with cancer after HTx (Weak Recommendation, Low-Quality Evidence).

Early weaning or low-dose maintenance corticosteroid therapy are both acceptable post-HTx with paucity of data to favour any single approach. However, in most recent trials of immunosuppression, corticosteroids are weaned 6-12 months

post HTx.[108] Corticosteroid regimens should be individualized according to the patient's risk of rejection and adverse effects.

RECOMMENDATION

29. We suggest weaning corticosteroids within 1-year post HTx for most patients (Weak Recommendation, Low-Quality Evidence).

Rejection surveillance

Endomyocardial biopsy. Endomyocardial biopsy remains the standard for AR surveillance post HTx despite its weak reliability.[109] Moreover, routine surveillance endomyocardial biopsy beyond the first year has poor clinical utility and is not cost effective.[110] The molecular microscope platform (MMDx) has shown promise in improving the diagnostic accuracy and utility of endomyocardial biopsy for detecting acute cellular rejection, antibody-mediated rejection, and other injury patterns through molecular phenotyping. The ongoing INTERHEART study (NCT02670408) should provide further insight.[111]

RECOMMENDATION

30. We recommend routine surveillance endomyocardial biopsy for 6-12 months post HTx (Strong Recommendation, Moderate-Quality Evidence).

Noninvasive surveillance strategies. Studies have shown that BNP or N-terminal proBNP are associated with biopsy rejection scores after 6 months post HTx,[112] although some inconsistencies exist.[113] High-sensitivity cardiac troponin might help rule out significant rejection.[114] Echocardiographic tissue Doppler and strain imaging parameters, especially speckle tracking, have shown promise for AR monitoring. Clinical implementation is problematic because of the lack of validated cutoff values and the unclear reliability early post HTx.[115] Cardiac magnetic resonance imaging parameters, especially T2 relaxation times, have good sensitivity and specificity in detecting AR beyond 6 months.[116] The ongoing Detection of Acute Graft Rejection in Heart Transplant Patients by Estimation of T2 (**D**étection des **R**ejets **A**igus de **G**reffe par **E**valuation du **T**2 [DRAGET]) study (NCT02261870) is evaluating the utility of cardiac magnetic resonance imaging for detecting AR in the first year post HTx.[117] Gene expression profiling from peripheral blood polynuclear cells has good negative predictive value for cellular rejection in low-risk patients beyond 6 months post HTx.[118] Although a small study showed no adverse outcomes when gene expression profiling is used early, starting at 55 days, evidence for use in the early phase is lacking.[119] Circulating donor-derived cell-free DNA measurements in patients post HTx appears to correlate with acute cellular rejection or antibody-mediated rejection, especially after 4 months post HTx.[120] A larger study including patients from 55 days to 5 years showed weaker correlation but still showed good negative predictive value.[121] MicroRNAs have been shown to differentiate rejection and nonrejection states.[122] However, in these small studies, their expression varied depending on type of rejection and tissue.[123]

RECOMMENDATION

31. We suggest using gene expression profiling as an alternative initial surveillance strategy in low-risk patients beyond 6 months post HTx (Weak Recommendation, Moderate-Quality Evidence).
32. We do not recommend circulating donor-derived cell-free DNA or microRNA testing as an alternative initial surveillance strategy for acute cellular rejection (Strong Recommendation, Moderate-Quality Evidence).

Values and preferences. Cardiac magnetic resonance imaging is safe and has very good resolution for structural and functional changes. However, the equipment and necessary expertise for this test are not broadly available. The lack of wide availability in Canada and relatively high expense of the currently available gene expression profiling platform (AlloMap; CareDx, Inc) might be an obstacle to its utility.

Rejection diagnosis and treatment

Pathological-based diagnosis of rejection using endomyocardial biopsy remains the gold standard (Supplemental Tables S3 and S4). Endomyocardial biopsy is performed for routine surveillance and when there is clinical suspicion of rejection. Rejection is classified as hyperacute, acute cellular rejection, or antibody-mediated rejection. Hyperacute rejection is usually fatal, occurring because of the presence of preformed anti-HLA class I antibodies against the donor. Routine performance of donor-recipient cross-matching at the time of transplantation has almost eliminated hyperacute rejection. Acute cellular rejection remains common in the first 3-6 months post HTx, occurring in 24% of HTx recipients. Approximately 13% will have significant acute cellular rejection in the first year post HTx to warrant treatment.[124] Antibody-mediated rejection is less common, affecting 10%-20% of HTx recipients.[125] Patients with either preformed or *de novo* anti-HLA antibodies are at increased risk of antibody-mediated rejection. Graft dysfunction is common with antibody-mediated rejection, accompanying up to two-thirds of early post HTx and 10%-15% of late antibody-mediated rejection episodes.[126]

Recommendation

33. We recommend standardized endomyocardial biopsy reporting of rejection according to the ISHLT grading for cellular and antibody-mediated rejection. (Strong Recommendation, Moderate-Quality Evidence).

Practical tip. Most rejection episodes are asymptomatic.

Treatment of rejection depends on the pathological severity, symptoms, allograft function, and timing post transplantation. Most patients with moderate ISHLT grade $\geq$ 2R cellular rejection are asymptomatic with normal hemodynamics, and can be treated with oral pulsed corticosteroids.[127] Symptomatic patients with ISHLT grade 2R or patients with 3R cellular rejection should be treated with intravenous pulsed corticosteroids. Patients with acute cellular rejection and hemodynamic compromise should be treated aggressively with pulse intravenous corticosteroids and thymoglobulin. Repeat endomyocardial biopsy is usually performed 7-14 days after treatment.

Treatment of antibody-mediated rejection is directed at removal of circulating antibodies and decreasing antibody production. Most treatment protocols use a combination of corticosteroids, plasmapheresis, and IVIG.[128-130] Newer, B-lymphocyte (rituximab)- and plasma cell (bortezomib)-depleting therapies have been used with variable reported success. Follow-up endomyocardial biopsy should be delayed for 2-4 weeks because of the delayed clearance of C4d stains. Additionally, after treating an episode of rejection, maintenance immunosuppression should be optimized, and graft function monitored.

RECOMMENDATION

34. We recommend oral pulsed corticosteroids for treatment of asymptomatic ISHLT 2R cellular rejection (Strong Recommendation, Low-Quality Evidence).
35. We recommend intravenous pulsed corticosteroids for treatment of ISHLT 3R or symptomatic ISHLT 2R cellular rejection (Strong Recommendation, Low-Quality Evidence).
36. We recommend thymoglobulin therapy for ISHLT 3R or 2R cellular rejection in the presence of graft dysfunction and/or hemodynamic compromise (Strong Recommendation, Low-Quality Evidence).
37. We recommend performing follow-up endomyocardial biopsy > 7-14 days after treatment of rejection (Strong Recommendation, Low-Quality Evidence).
38. We suggest treatment of antibody-mediated rejection for ISHLT pathologic antibody mediated rejection (pAMR) $\geq$ 2 or pAMR 1 with graft dysfunction and/or symptoms (Weak Recommendation, Low-Quality Evidence).
39. We suggest treatment for antibody-mediated rejection include a combination of intravenous pulsed corticosteroids, plasmapheresis, IVIG and/or thymoglobulin (Weak Recommendation, Low-Quality Evidence).
40. We suggest consideration of adjunctive rituximab and/or bortezomib for treatment of antibody-mediated rejection (Weak Recommendation, Low-Quality Evidence).

HLA-antibody/DSA monitoring and management

The prevalence of DSA post HTx ranges between 15% and 33%.[131] Although DSA is associated with rejection, CAV, graft dysfunction, and mortality, post transplantation DSA monitoring and treatment in stable grafts have not been proven to improve outcomes.[132] Moreover, available treatments are costly and not benign. Additionally, evaluation for rejection, graft function, and CAV are important to determine the effect of DSA (Fig. 1). In general, early antibody-mediated rejection is more responsive to treatment and therefore, testing in the early postoperative period is recommended for patients with increased immune risk such as those with known DSA at the time of transplantation or a history of sensitizing events.[133] Monitoring for DSA at later time points and in otherwise stable low immune risk recipients is more controversial.

RECOMMENDATION

41. We recommend routine post HTx DSA testing if DSA has been crossed at the time of transplantation (Strong Recommendation, High-Quality Evidence).
42. We suggest post HTx DSA testing in stable recipients without DSA before transplantation (Weak Recommendation, Low-Quality Evidence).

Values and preferences. Patients with preformed DSA are at risk of an amnestic response and resulting high levels of DSA with increased risk for rejection and graft dysfunction. Detection of *de novo* DSA identifies increased-risk individuals but many patients remain stable and it is unknown whether intervention for DSA changes outcomes.

Practical tip. Suggested frequency of DSA testing in stable grafts is at week 1 and 2, months 1, 3, 6, 9, and 12, followed by annually post transplantation.

RECOMMENDATION

43. We recommend *de novo* DSA be confirmed within 2-3 months post detection (Strong Recommendation, Moderate-Quality Evidence).
44. We suggest assessment for rejection, graft function, and CAV if DSA is persistent (Weak Recommendation, Moderate-Quality Evidence).

Values and preferences. The measurement of antibody median fluorescence intensity level has some correlation with outcomes and might guide response to treatment. Median fluorescence intensity alone is not ideal and additional assays including titers, complement fixing assays, and immunoglobulin G subclasses are often performed to identify antibodies that might pose a greater risk. Lower level DSAs are still associated with inferior outcomes and multiple weak antibodies to the same target might bind complement *in vivo* although the assay might be negative.

Practical tip. If additional information is required for clinical care, consultation with the histocompatibility laboratory team is recommended to determine if further testing is indicated.

RECOMMENDATION

45. We suggest optimization of maintenance immunosuppression if DSA is detected (Weak Recommendation, Low-Quality Evidence).
46. We recommend treatment of DSA if there is evidence of antibody-mediated rejection or graft dysfunction (Strong Recommendation, Moderate-Quality Evidence).

Values and preferences. No evidence exists to guide management of DSA, but at a minimum, review and optimization of immunosuppression is warranted. If there is rejection, immunomodulating agents should be added. The presence of CAV might prompt conversion/additional use of PSIs. Because of the poor prognosis associated with graft dysfunction and DSA, many would elect to treat despite the lack of evidence.

CAV

CAV is prevalent and a major determinant of long-term survival after HTx; surveillance and prevention are the cornerstone of management.[6] Imaging evaluation is a challenge because of preserved coronary calibre in early disease and diffuse epicardial and microvascular involvement. Up to 5 years post transplantation, annual invasive coronary angiography and intravascular ultrasound are preferred to diagnose early-stage CAV, and detect donor atherosclerosis and rapidly progressive CAV (intravascular ultrasound maximal intimal thickness $\geq$ 0.5 mm increase in first transplantation year), which are predictive of cardiac events and disease progression.[134,135] High-resolution optical coherence tomography improves evaluation of intimal hyperplasia and plaque composition. Intracoronary flow measures of microvascular endothelial dysfunction such as coronary flow reserve and index of microcirculatory resistance are predictors of CAV and cardiovascular outcomes.[136,137] Prospective studies are needed to define the role of optical coherence tomography and intracoronary flow in CAV screening. There is no established robust noninvasive technique for CAV surveillance. Commonly used stress echocardiography and radionuclide perfusion imaging have modest accuracy for angiographic CAV but high negative predictive value for adverse cardiac events.[138,139] Computed tomography coronary angiography has high sensitivity, specificity, and negative predictive value for > 50% angiographic stenosis but reduced sensitivity compared with intravascular ultrasound.[140] Myocardial blood flow quantification using positron emission tomography has good diagnostic accuracy for CAV but is less widely available.[141,142]

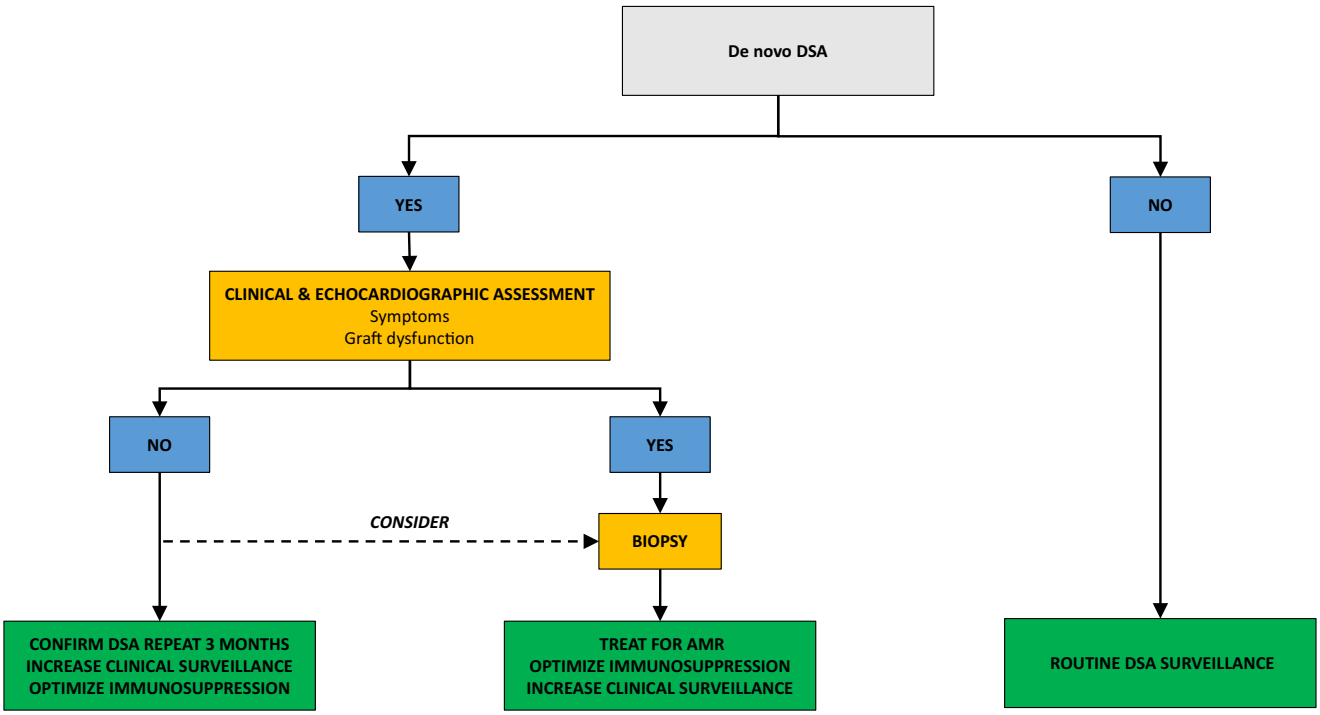

Figure 1. Post transplantation *de novo* donor-specific antibody (DSA) management. Routine surveillance of DSA is suggested at week 1 and 2, months 1, 3, 6, 9, and 12, followed by annually post transplantation. Patients with newly detected DSA post transplantation should be evaluated for clinical symptoms, evidence of allograft dysfunction, and rejection. Antibody-mediated rejection (AMR) should be treated if detected on endomyocardial biopsy. All patients with DSA should have optimization of maintenance immunosuppression and increased clinical surveillance (2 assessments of graft function 1-3 months apart).

RECOMMENDATION

47. We recommend invasive coronary angiography and intravascular ultrasound for CAV surveillance up to 5 years post transplantation (Strong Recommendation, Moderate-Quality Evidence).
48. We suggest invasive coronary angiography and intravascular ultrasound at 6-12 weeks post transplantation to detect donor atherosclerotic disease and rapidly progressive CAV (Weak Recommendation, Moderate-Quality Evidence).

Values and preferences. Screening for CAV is typically performed annually, individualized to donor and recipient characteristics. An invasive strategy with intracoronary imaging to visualize the vessel wall is preferred early post transplantation to improve sensitivity for detecting early CAV and for prognostication but is expensive and not widely available. Patients with kidney disease should undergo less frequent invasive angiography. A noninvasive strategy is preferred in the long term post transplantation with the choice of testing according to institutional expertise and preference. This considers the high prevalence of CAV with increasing time from transplantation as well as reduced accuracy of commonly available noninvasive tests.

Statins and PSIs reduce the incidence of CAV.[101,143,144] Other pharmacologic treatments suggested to reduce CAV development include calcium antagonists, angiotensin converting enzyme inhibitors, and aspirin.[145,146] In randomized controlled studies, *de novo* PSI treatment with CNI reduction or withdrawal decreased plaque progression.[101,144] Attenuation of CAV progression is greater when PSIs are initiated early, < 2 years post transplantation.[147,148] For patients with established CAV, percutaneous coronary intervention is effective, with drug eluting stents reducing stent restenosis but not improving survival.[149] Retransplantation is often the only option in advanced CAV but reserved for patients with advanced disease with allograft dysfunction (Fig. 2).[150]

RECOMMENDATION

49. We recommend aggressive management of cardiovascular risk factors including hypertension, diabetes, and hyperlipidemia for prevention of CAV (Strong Recommendation, Low-Quality Evidence).
50. We recommend a statin regardless of serum lipid levels (Strong Recommendation, High-Quality Evidence).
51. We suggest angiotensin converting enzyme inhibitor or calcium channel blocker as first-line therapies for hypertension because of possible benefits of reducing CAV (Weak Recommendation, Low-Quality Evidence).
52. We suggest aspirin for prevention of CAV (Weak Recommendation, Low-Quality Evidence).
53. We recommend PSIs for prevention and treatment of CAV in patients < 5 years post transplantation (Strong Recommendation, High-Quality Evidence).

Values and preferences. Most *de novo* PSI studies used everolimus, which is not available in Canada. Available evidence supports early institution of PSIs with late treatment less effective for attenuating progression of CAV.

54. We suggest suitable patients with CAV undergo percutaneous revascularization, and retransplantation be considered for severe CAV and allograft dysfunction (Weak Recommendation, Moderate-Quality Evidence).

Long-term noncardiac care post HTx

Long-term noncardiac care post HTx is briefly summarized in Table 3, including *de novo* malignancies, vascular disease, and infection monitoring.

***De novo* malignancies.** Compared with the general population, HTx patients are at a 2- to 4-fold higher risk of malignancy, and *de novo* malignancy is the leading cause of mortality beyond 3 years post transplantation, accounting for 7.8% of deaths after 5 years.[151-153] The 2018 ISHLT registry showed increasing trends in the cumulative incidence of *de novo* malignancies after HTx.[153] Skin, post transplantation lymphoproliferative disorders (PTLD), and prostate and lung cancers are the most common causes of *de novo* malignancies after HTx.[153,154] Risk factors associated with *de novo* malignancies include older age at the time of transplantation, male sex, and aggressive immunosuppressive therapy. There are limited data to guide recommendations for malignancy screening post HTx.[105,155]

RECOMMENDATION

55. We recommend that general population screening for breast, cervical, colon, and prostate cancer be applied to HTx recipients (Strong Recommendation, Low-Quality Evidence).

Values and preferences. There is no evidence to support reduction of immunosuppression in patients with nonlymphoid solid tumours, however, use of maintenance immunosuppression should be minimized.

Skin malignancy. Early detection of skin cancer can facilitate early removal that might in turn improve the post diagnosis survival among transplant recipients.[156] Annual skin cancer screening is recommended, with increased surveillance frequency guided by individual risk.[153,157,158]

RECOMMENDATION

56. We recommend HTx recipients have annual skin cancer surveillance by a family physician or a specialist (Strong Recommendation, Low-Quality Evidence).

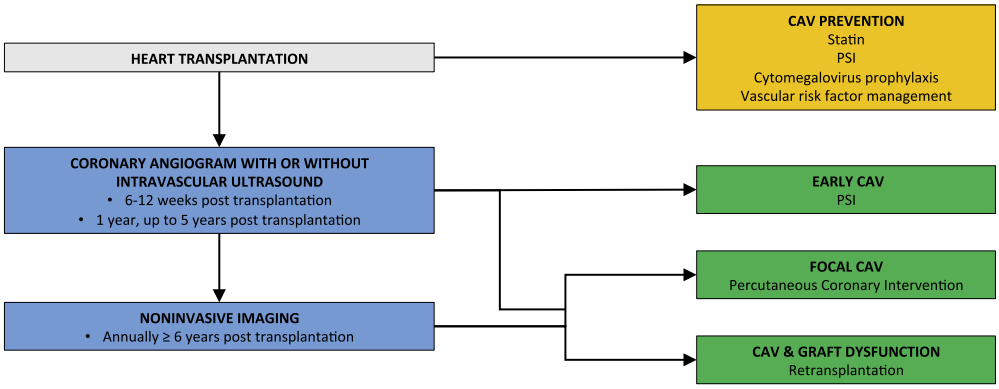

Figure 2. Cardiac allograft vasculopathy (CAV) surveillance and management. Invasive coronary angiography and intravascular ultrasound are suggested at 6-12 weeks post transplantation to detect donor disease and recommended at 1 year and up to 5 years post transplantation to detect early CAV. Beyond 5 years, annual noninvasive imaging according to institutional preference can guide the need for invasive testing. Preventive therapy for CAV are initiated immediately post transplantation, and include statin, proliferation signal inhibitor (PSI), and aggressive risk factor management. Treatments for CAV include conversion to PSI to delay progression of disease, particularly for early CAV < 5 years post transplantation; percutaneous coronary intervention for focal obstructive disease; and retransplantation in selected patients with severe CAV and associated allograft dysfunction.

PTLD. HTx patients who have received induction therapy or high-dose immunosuppression, those with Epstein-Barr virus donor-recipient mismatch are at higher risk of PTLD.[159] PTLD has a mortality rate of up to 70% within the first year of diagnosis.[160] Early diagnosis is key to improving survival. Preventative strategies including recommendations on screening are lacking. Furthermore, there is equipoise surrounding whether an immunosuppression reduction reduces PTLD incidence and improves prognosis.[161] Treatment for PTLD has traditionally included reduction of immunosuppression and in the contemporary era anti-CD20 rituximab-based regimens.[161]

RECOMMENDATION

57. We do not recommend routine PTLD screening for asymptomatic HTx recipients (Strong Recommendation, Low-Quality Evidence).

Vascular complications. HTx patients are at risk of accelerated vascular disease due to adverse effects of immunosuppressive therapy in combination with coexistent vascular risk factors.[162] Cerebrovascular complications occur in 5%-11% of patients after HTx.[163-165] Ischemic stroke is the most common cause, accounting for 60% of cerebrovascular complications. Approximately 20% of cerebrovascular complications occur in the immediate postoperative period within 2 weeks of HTx.[164,166] Previous stroke is the key risk factor associated with increased risk of cerebrovascular complications post HTx.[167] Peripheral vascular disease occurs in 10% of HTx patients.[164] Patients with symptomatic peripheral vascular disease before HTx have a lower survival rate compared with patients without peripheral vascular disease; 1-, 5-, and 10-year survival rates are 91.5% vs 94.9%, 74.8% vs 82.6%, 48.6% vs 54.7%, respectively.[168] Furthermore, the prevalence of abdominal aortic aneurysm is reported at 2%-10%, with rupture rates of 11%-38%.[169] The role of vascular screening post HTx in asymptomatic patients is unclear.[170] Targeting modifiable risk factors including hypertension,

Table 3. Post heart transplantation noncardiac surveillance

	Recommended screening	Test	Interval	Comment
De novo malignancies				
Breast cancer	General population screening	Mammogram	Every 2 years	Women age 54-75 years
Cervical cancer	General population screening	Pap smear	Every 3 years	Women age 21-69 years
Prostate cancer		Not recommended		
Colon cancer	General population screening	Fecal occult blood test	Every 2 years	Men and women age 50-74 years
Skin cancer	High-risk population screening	Skin check	Every year	Increase screening frequency for high risk: skin type, high sun exposure, history of skin cancer
Vascular disease				
CVD and PVD		Not recommended		
Infection monitoring				
CMV	High-risk population screening	CMV QNAT	Weekly for 12 weeks	After completion of universal prophylaxis
EBV		Not recommended		
PJP		Not recommended		

CMV, cytomegalovirus; CVD, cerebrovascular disease; EBV, Epstein Barr virus; PJP, *Pneumocystis jirovecii* pneumonia; PVD, peripheral vascular disease; QNAT, quantitative nucleic acid amplification testing.

diabetes, hyperlipidemia, smoking and alcohol cessation are important for reducing vascular complications.[171]

RECOMMENDATION

58. We recommend aggressive risk factor management, including optimizing blood pressure, serum lipid level, and glucose as well as smoking and alcohol cessation (Strong Recommendation, Low-Quality Evidence).

Infection monitoring after HTx. Infectious complications are a major cause of death, accounting for 14% of deaths during the initial 3 years and 11% thereafter.[153]

Cytomegalovirus infection. Cytomegalovirus infections account for 1% of deaths and approximately 3% of infectious complication-related death within 1 year after HTx.[6] Universal cytomegalovirus prophylaxis in high-risk recipients using valganciclovir or ganciclovir post HTx for 3-6 months significantly reduces the risk of cytomegalovirus disease.[153,172,173] Patients at high risk of cytomegalovirus infection include donor-positive (D^+) and recipient-negative (R^-) serostatus and higher levels of immunosuppression, particularly those receiving antilymphocyte depleting induction. Surveillance with cytomegalovirus quantitative nucleic acid testing should be undertaken after completion of universal prophylaxis and should be used to guide the need for preemptive therapy.[173-175] Either prophylaxis or preemptive therapy can be used to prevent cytomegalovirus infection in intermediate-risk patients (R^+ without lymphocyte-depleting induction).[153,173]

RECOMMENDATION

59. We recommend universal cytomegalovirus prophylaxis for high-risk patients (ie, D^+/R^- and R^+ receiving lymphocyte-depleting induction) using valganciclovir post HTx for 3-6 months. Cytomegalovirus prophylaxis for D^-/R^- is not recommended (Strong Recommendation, Moderate-Quality Evidence).
60. We recommend universal cytomegalovirus prophylaxis or preemptive therapy for intermediate-risk patients (R^+ not receiving lymphocyte depletion therapy) using valganciclovir post HTx for 3 months (Strong Recommendation, Moderate-Quality Evidence).
61. We recommend weekly cytomegalovirus quantitative nucleic acid testing for 12 weeks after universal prophylaxis. A preemptive treatment approach should be adopted for viral load past institutional-defined threshold levels (Strong Recommendation, Low-Quality Evidence).

Epstein-Barr virus infection. There is no clear evidence supporting universal Epstein-Barr virus polymerase chain reaction monitoring post HTx. However, monitoring might benefit high-risk Epstein-Barr virus D^+ and R^- patients. An increasing Epstein-Barr virus polymerase chain reaction in this patient population identifies patients at risk of PTLD.

Pneumocystis jirovecii pneumonia infection. P jirovecii pneumonia infection occurs in 2%-10% of HTx patients, and is associated with poor survival.[176-178] Universal prophylaxis, using trimethoprim-sulfamethoxazole for 1 year reduced the incidence of *P jirovecii* pneumonia and related mortality by 85% and 83%, respectively.[179] No differences in incidence, mortality, or adverse events have been shown for daily vs thrice-weekly prophylaxis.[179] The highest risk of *P jirovecii* pneumonia is during the initial 6 months post transplantation. Because of the low $< 0.6\%$ incidence of *P jirovecii* pneumonia during the second year, universal prophylaxis is typically limited to 1 year.[176,179]

RECOMMENDATION

62. We recommend universal *P jirovecii* pneumonia prophylaxis with trimethoprim-sulfamethoxazole for 1 year minimum after HTx (Strong Recommendation, Moderate-Quality Evidence).

Practical tip. Patients with a contraindication to trimethoprim-sulfamethoxazole such as sulfa allergy may be treated with dapsone, pentamidine, or atovaquone.

Psychosocial depression, family caregiver burden

Recipients. HTx recipients and their caregivers experience a range of mental health problems post transplantation. There is little evidence to guide practitioners in their care and much of the literature is > 10 years old. Depression and anxiety are the most common psychiatric disorders post transplantation. There is evidence that depression is an independent risk factor for long-term outcome,[180,181] but no studies have examined the effect of treating depression on mortality. There is increasing interest in post-traumatic stress disorder secondary to transplantation.[182]

RECOMMENDATION

63. We recommend HTx recipients be asked about mental health symptoms and substance use as part of standard follow-up visits (Strong Recommendation, Moderate-Quality Evidence).
64. We recommend HTx recipients describing mental health or addiction symptoms be referred for further evaluation and treatment (Strong Recommendation, Moderate-Quality Evidence).

Values and preferences. Optimizing quality of life and reducing morbidity and mortality is the focus of post transplantation care. Identifying and then managing mental health and addiction symptoms is integral to this goal.

Caregivers. Caregivers of HTx recipients are vulnerable to the development of depressive, anxiety, and post-traumatic stress disorders[181] as well as declining physical functioning and increased pain.[183] Caregiver general health is a significant, independent predictor of patients' mortality risk.[183]

RECOMMENDATION

65. We recommend caregivers of potential HTx recipients be made aware of the potential effect on their own health and encouraged to obtain professional support to optimize their own health (Strong Recommendation, Moderate-Quality Evidence).

Values and preferences. Caregiver support is essential to optimal post transplantation recipient outcomes.

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References

1. Ross H, Hendry P, Dipchand A, et al. 2001 Canadian Cardiovascular Society consensus conference on cardiac transplantation. Can J Cardiol 2003;19:620-54.
2. Haddad H, Isaac D, Legare JF, et al. Canadian Cardiovascular Society consensus conference update on cardiac transplantation 2008: executive summary. Can J Cardiol 2009;25:197-205.
3. Moayedi Y, Alhussein M, Duero Posada JG, et al. New horizons on the 50th anniversary of heart transplantation in Canada: "Where there is death, there is hope". Can J Cardiol 2018;34:694-5.
4. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6.
5. Lund LH, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: thirtieth official adult heart transplant report–2013; focus theme: age. J Heart Lung Transplant 2013;32:951-64.
6. Khush KK, Cherikh WS, Chambers DC, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: thirty-fifth adult heart transplantation report-2018; focus theme: multiorgan transplantation. J Heart Lung Transplant 2018;37:1155-68.
7. Goldstein DJ, Bello R, Shin JJ, et al. Outcomes of cardiac transplantation in septuagenarians. J Heart Lung Transplant 2012;31:679-85.
8. Cooper LB, Lu D, Mentz RJ, et al. Cardiac transplantation for older patients: characteristics and outcomes in the septuagenarian population. J Heart Lung Transplant 2016;35:362-9.
9. Mehra MR, Canter CE, Hannan MM, et al. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year update. J Heart Lung Transplant 2016;35:1-23.
10. Sze S, Pellicori P, Zhang J, Weston J, Clark AL. Identification of frailty in chronic heart failure. JACC Heart Fail 2019;7:291-302.
11. Fang JC, Ewald GA, Allen LA, et al. Advanced (stage D) heart failure: a statement from the Heart Failure Society of America Guidelines Committee. J Card Fail 2015;21:519-34.
12. Jha SR, Hannu MK, Gore K, et al. Cognitive impairment improves the predictive validity of physical frailty for mortality in patients with advanced heart failure referred for heart transplantation. J Heart Lung Transplant 2016;35:1092-100.
13. Maurer MS, Horn E, Reyentovich A, et al. Can a left ventricular assist device in individuals with advanced systolic heart failure improve or reverse frailty? J Am Geriatr Soc 2017;65:2383-90.
14. Mauthner O, Claes V, Deschodt M, et al. Handle with care: a systematic review on frailty in cardiac care and its usefulness in heart transplantation. Transplant Rev (Orlando) 2017;31:218-24.
15. Rolfson DB, Majumdar SR, Tsuyuki RT, Tahir A, Rockwood K. Validity and reliability of the Edmonton Frail Scale. Age Ageing 2006;35:526-9.
16. Weiss ES, Allen JG, Russell SD, Shah AS, Conte JV. Impact of recipient body mass index on organ allocation and mortality in orthotopic heart transplantation. J Heart Lung Transplant 2009;28:1150-7.
17. Weber DJ, Hashmi ZA, Gracon AS, et al. Recipient body mass index and age interact to impact survival after heart transplantation. Clin Transplant 2014;28:1279-86.
18. Russo MJ, Hong KN, Davies RR, et al. The effect of body mass index on survival following heart transplantation: do outcomes support consensus guidelines? Ann Surg 2010;251:144-52.
19. Clerkin KJ, Naka Y, Mancini DM, Colombo PC, Topkara VK. The impact of obesity on patients bridged to transplantation with continuous-flow left ventricular assist devices. JACC Heart Fail 2016;4:761-8.
20. Butler J, Stankewicz MA, Wu J, et al. Pre-transplant reversible pulmonary hypertension predicts higher risk for mortality after cardiac transplantation. J Heart Lung Transplant 2005;24:170-7.
21. Delgado JF, Gomez-Sanchez MA, Saenz de la Calzada C, et al. Impact of mild pulmonary hypertension on mortality and pulmonary artery pressure profile after heart transplantation. J Heart Lung Transplant 2001;20:942-8.
22. Kanwar M, Raina A, Aponte MP, Benza R. Pulmonary hypertension in potential heart transplant recipients: current treatment strategies. Curr Opin Organ Transplant 2015;20:570-6.
23. Krishnamurthy Y, Cooper LB, Parikh KS, et al. Pulmonary hypertension in the era of mechanical circulatory support. ASAIO J 2016;62:505-12.
24. John R, Liao K, Kamdar F, et al. Effects on pre- and post-transplant pulmonary hemodynamics in patients with continuous-flow left ventricular assist devices. J Thorac Cardiovasc Surg 2010;140:447-52.
25. Jabbour A, Keogh A, Hayward C, Macdonald P. Chronic sildenafil lowers transpulmonary gradient and improves cardiac output allowing successful heart transplantation. Eur J Heart Fail 2007;9:674-7.
26. De Santo LS, Romano G, Maiello C, et al. Pulmonary artery hypertension in heart transplant recipients: how much is too much? Eur J Cardiothorac Surg 2012;42:864-9 [discussion: 9-70].
27. Perez-Villa F, Farrero M, Sionis A, Castel A, Roig E. Therapy with sildenafil or bosentan decreases pulmonary vascular resistance in patients

ineligible for heart transplantation because of severe pulmonary hypertension. J Heart Lung Transplant 2010;29:817-8.

28. Feldman D, Pamboukian SV, Teuteberg JJ, et al. The 2013 International Society for Heart and Lung Transplantation guidelines for mechanical circulatory support: executive summary. J Heart Lung Transplant 2013;32:157-87.

29. Dew MA, DiMartini AF, Dobbels F, et al. The 2018 ISHLT/APM/AST/ICCAC/STSW recommendations for the psychosocial evaluation of adult cardiothoracic transplant candidates and candidates for long-term mechanical circulatory support. J Heart Lung Transplant 2018;37:803-23.

30. Government of Canada. Justice Laws Website. Cannabis Act. Available at: https://laws-lois.justice.gc.ca/eng/acts/c-24.5/page-1.html. Accessed March 27, 2019.

31. Ravi D, Ghasemiesfe M, Korenstein D, Cascino T, Keyhani S. Associations between marijuana use and cardiovascular risk factors and outcomes: a systematic review. Ann Intern Med 2018;168:187-94.

32. Levi ME, Montague BT, Thurstone C, et al. Marijuana use in transplantation: a call for clarity. Clin Transplant 2019;33:e13456.

33. Stout SM, Cimino NM. Exogenous cannabinoids as substrates, inhibitors, and inducers of human drug metabolizing enzymes: a systematic review. Drug Metab Rev 2014;46:86-95.

34. Hauser N, Sahai T, Richards R, Roberts T. High on cannabis and calcineurin inhibitors: a word of warning in an era of legalized marijuana. Case Rep Transplant 2016;2016:4028492.

35. Sousa M, Monohan G, Rajagopalan N, Grigorian A, Guglin M. Heart transplantation in cardiac amyloidosis. Heart Fail Rev 2017;22:317-27.

36. Gray Gilstrap L, Niehaus E, Malhotra R, et al. Predictors of survival to orthotopic heart transplant in patients with light chain amyloidosis. J Heart Lung Transplant 2014;33:149-56.

37. Lee JY, Lim SH, Kim SJ, et al. Bortezomib, melphalan, and prednisolone combination chemotherapy for newly diagnosed light chain (AL) amyloidosis. Amyloid 2014;21:261-6.

38. Scott EC, Heitner SB, Dibb W, et al. Induction bortezomib in Al amyloidosis followed by high dose melphalan and autologous stem cell transplantation: a single institution retrospective study. Clin Lymphoma Myeloma Leuk 2014;14:424-430.e1.

39. Davis MK, Kale P, Liedtke M, et al. Outcomes after heart transplantation for amyloid cardiomyopathy in the modern era. Am J Transplant 2015;15:650-8.

40. Davis MK, Lee PH, Witteles RM. Changing outcomes after heart transplantation in patients with amyloid cardiomyopathy. J Heart Lung Transplant 2015;34:658-66.

41. Varr BC, Liedtke M, Arai S, et al. Heart transplantation and cardiac amyloidosis: approach to screening and novel management strategies. J Heart Lung Transplant 2012;31:325-31.

42. Thenappan T, Fedson S, Rich J, et al. Isolated heart transplantation for familial transthyretin (TTR) V122I cardiac amyloidosis. Amyloid 2014;21:120-3.

43. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. N Engl J Med 2018;379:1007-16.

44. Radovancevic B, McGiffin DC, Kobashigawa JA, et al. Retransplantation in 7,290 primary transplant patients: a 10-year multi-institutional study. J Heart Lung Transplant 2003;22:862-8.

45. Mahle WT, Vincent RN, Kanter KR. Cardiac retransplantation in childhood: analysis of data from the United Network for Organ Sharing. J Thorac Cardiovasc Surg 2005;130:542-6.

46. Shuhaiber JH, Kim JB, Hur K, et al. Comparison of survival in primary and repeat heart transplantation from 1987 through 2004 in the United States. Ann Thorac Surg 2007;83:2135-41.

47. Rizvi SA, Luc JGY, Choi JH, et al. Outcomes and survival following heart retransplantation for cardiac allograft failure: a systematic review and meta-analysis. Ann Cardiothorac Surg 2018;7:12-8.

48. Assenza GE, Graham DA, Landzberg MJ, et al. MELD-XI score and cardiac mortality or transplantation in patients after Fontan surgery. Heart 2013;99:491-6.

49. Besik J, Szarszoi O, Hegarova M, et al. Non-Fontan adult congenital heart disease transplantation survival is equivalent to acquired heart disease transplantation survival. Ann Thorac Surg 2016;101:1768-73.

50. Bhama JK, Shulman J, Bermudez CA, et al. Heart transplantation for adults with congenital heart disease: results in the modern era. J Heart Lung Transplant 2013;32:499-504.

51. Cohen S, Houyel L, Guillemain R, et al. Temporal trends and changing profile of adults with congenital heart disease undergoing heart transplantation. Eur Heart J 2016;37:783-9.

52. Haberger S, Hauser M, Braun SL, et al. Prognostic value of plasma B-type natriuretic peptide in the long-term follow-up of patients with transposition of the great arteries with morphologic right systemic ventricle after atrial switch operation. Circ J 2015;79:2677-81.

53. Inuzuka R, Diller GP, Borgia F, et al. Comprehensive use of cardiopulmonary exercise testing identifies adults with congenital heart disease at increased mortality risk in the medium term. Circulation 2012;125:250-9.

54. Kempny A, Dimopoulos K, Uebing A, et al. Reference values for exercise limitations among adults with congenital heart disease. Relation to activities of daily life–single centre experience and review of published data. Eur Heart J 2012;33:1386-96.

55. Koyak Z, de Groot JR, Krimly A, et al. Cardiac resynchronization therapy in adults with congenital heart disease. Europace 2018;20:315-22.

56. Lewis M, Ginns J, Schulze C, et al. Outcomes of adult patients with congenital heart disease after heart transplantation: impact of disease type, previous thoracic surgeries, and bystander organ dysfunction. J Card Fail 2016;22:578-82.

57. Robinson JA, Driscoll DJ, O'Leary PW, et al. Cardiac and multiorgan transplantation for end-stage congenital heart disease. Mayo Clin Proc 2014;89:478-83.

58. Westhoff-Bleck M, Podewski E, Tutarel O, et al. Prognostic value of NT-proBNP in patients with systemic morphological right ventricles: a single-centre experience. Int J Cardiol 2013;169:433-8.

59. Van De Bruaene A, Hickey EJ, Kovacs AH, et al. Phenotype, management and predictors of outcome in a large cohort of adult congenital heart disease patients with heart failure. Int J Cardiol 2018;252:80-7.

60. Burchill LJ, Edwards LB, Dipchand AI, Stehlik J, Ross HJ. Impact of adult congenital heart disease on survival and mortality after heart transplantation. J Heart Lung Transplant 2014;33:1157-63.

61. Davies RR, Russo MJ, Yang J, et al. Listing and transplanting adults with congenital heart disease. Circulation 2011;123:759-67.

62. Everitt MD, Donaldson AE, Stehlik J, et al. Would access to device therapies improve transplant outcomes for adults with congenital heart

disease? Analysis of the United Network for Organ Sharing (UNOS). J Heart Lung Transplant 2011;30:395-401.

63. Gelow JM, Song HK, Weiss JB, Mudd JO, Broberg CS. Organ allocation in adults with congenital heart disease listed for heart transplant: impact of ventricular assist devices. J Heart Lung Transplant 2013;32:1059-64.

64. Hsich EM, Rogers JG, McNamara DM, et al. Does survival on the heart transplant waiting list depend on the underlying heart disease? JACC Heart Fail 2016;4:689-97.

65. Karamlou T, Diggs BS, Welke K, et al. Impact of single-ventricle physiology on death after heart transplantation in adults with congenital heart disease. Ann Thorac Surg 2012;94:1281-7 [discussion: 7-8].

66. Karamlou T, Hirsch J, Welke K, et al. A United Network for Organ Sharing analysis of heart transplantation in adults with congenital heart disease: outcomes and factors associated with mortality and retransplantation. J Thorac Cardiovasc Surg 2010;140:161-8.

67. Krishnamurthy Y, Cooper LB, Lu D, et al. Trends and outcomes of patients with adult congenital heart disease and pulmonary hypertension listed for orthotopic heart transplantation in the United States. J Heart Lung Transplant 2016;35:619-24.

68. Maxwell BG, Wong JK, Sheikh AY, Lee PH, Lobato RL. Heart transplantation with or without prior mechanical circulatory support in adults with congenital heart disease. Eur J Cardiothorac Surg 2014;45:842-6.

69. Patel ND, Weiss ES, Allen JG, et al. Heart transplantation for adults with congenital heart disease: analysis of the United network for organ sharing database. Ann Thorac Surg 2009;88:814-21 [discussion: 21-2].

70. Shah DK, Deo SV, Althouse AD, et al. Perioperative mortality is the Achilles heel for cardiac transplantation in adults with congenital heart disease: evidence from analysis of the UNOS registry. J Card Surg 2016;31:755-64.

71. Doumouras BS, Alba AC, Foroutan F, et al. Outcomes in adult congenital heart disease patients undergoing heart transplantation: a systematic review and meta-analysis. J Heart Lung Transplant 2016;35:1337-47.

72. Ross HJ, Law Y, Book WM, et al. Transplantation and mechanical circulatory support in congenital heart disease: a scientific statement from the American Heart Association. Circulation 2016;133:802-20.

73. Chambers DC, Cherikh WS, Goldfarb SB, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: thirty-fifth adult lung and heart-lung transplant report-2018; focus theme: multiorgan transplantation. J Heart Lung Transplant 2018;37:1169-83.

74. Schaffer JM, Chiu P, Singh SK, et al. Heart and combined heart-kidney transplantation in patients with concomitant renal insufficiency and end-stage heart failure. Am J Transplant 2014;14:384-96.

75. Schaffer JM, Chiu P, Singh SK, et al. Combined heart-liver transplantation in the MELD era: do waitlisted patients require exception status? Am J Transplant 2014;14:647-59.

76. Kilic A, Grimm JC, Whitman GJ, et al. The survival benefit of simultaneous heart-kidney transplantation extends beyond dialysis-dependent patients. Ann Thorac Surg 2015;99:1321-7.

77. Cannon RM, Hughes MG, Jones CM, Eng M, Marvin MR. A review of the United States experience with combined heart-liver transplantation. Transpl Int 2012;25:1223-8.

78. Bradley EA, Pinyoluksana KO, Moore-Clingenpeel M, Miao Y, Daniels C. Isolated heart transplant and combined heart-liver transplant in adult congenital heart disease patients: insights from the United Network of Organ Sharing. Int J Cardiol 2017;228:790-5.

79. D'Souza BA, Fuller S, Gleason LP, et al. Single-center outcomes of combined heart and liver transplantation in the failing Fontan. Clin Transplant 2017;31:e12892.

80. Clarke B, Ducharme A, Giannetti N, et al. Multicenter evaluation of a national organ sharing policy for highly sensitized patients listed for heart transplantation in Canada. J Heart Lung Transplant 2017;36:491-8.

81. Gazdic T, Malek I, Pagacova L, et al. Safety and efficacy of immunoadsorption in heart transplantation program. Transplant Proc 2016;48:2792-6.

82. Leech SH, Lopez-Cepero M, LeFor WM, et al. Management of the sensitized cardiac recipient: the use of plasmapheresis and intravenous immunoglobulin. Clin Transplant 2006;20:476-84.

83. Kobashigawa JA, Patel JK, Kittleson MM, et al. The long-term outcome of treated sensitized patients who undergo heart transplantation. Clin Transplant 2011;25:E61-7.

84. Patel J, Dilibero D, Kittleson M, et al. Terminal complement inhibition for highly sensitized patients undergoing heart transplantation - doable? J Heart Lung Transplant 2015;34:S31.

85. Riella LV, Safa K, Yagan J, et al. Long-term outcomes of kidney transplantation across a positive complement-dependent cytotoxicity crossmatch. Transplantation 2014;97:1247-52.

86. Woodle ES, Shields AR, Ejaz NS, et al. Prospective iterative trial of proteasome inhibitor-based desensitization. Am J Transplant 2015;15:101-18.

87. Kahwaji J, Jordan SC, Najjar R, et al. Six-year outcomes in broadly HLA-sensitized living donor transplant recipients desensitized with intravenous immunoglobulin and rituximab. Transpl Int 2016;29:1276-85.

88. Montgomery RA, Lonze BE, King KE, et al. Desensitization in HLA-incompatible kidney recipients and survival. N Engl J Med 2011;365:318-26.

89. May LJ, Yeh J, Maeda K, et al. HLA desensitization with bortezomib in a highly sensitized pediatric patient. Pediatr Transplant 2014;18:E280-2.

90. Nakamura Y, Yoshioka D, Miyagawa S, et al. Successful heart transplantation after desensitization in a patient with extremely high panel-reactive antibody levels and pretransplant donor-specific antibody: a case report. Transplant Proc 2018;50:4067-70.

91. Patel J, Everly M, Chang D, et al. Reduction of alloantibodies via proteasome inhibition in cardiac transplantation. J Heart Lung Transplant 2011;30:1320-6.

92. Schaffer JM, Singh SK, Reitz BA, et al. Heart transplant graft survival is improved after a reduction in panel reactive antibody activity. J Thorac Cardiovasc Surg 2013;145:555-64 [discussion: 64-5].

93. Alhussein M, Moayedi Y, Posada JD, Tinckam K, Ross HJ. Perioperative desensitization for highly sensitized heart transplant patients. J Heart Lung Transplant 2018;37:667-70.

94. Zuckermann A, Keogh A, Crespo-Leiro MG, et al. Randomized controlled trial of sirolimus conversion in cardiac transplant recipients with renal insufficiency. Am J Transplant 2012;12:2487-97.

95. Kaczmarek I, Zaruba MM, Beiras-Fernandez A, et al. Tacrolimus with mycophenolate mofetil or sirolimus compared with calcineurin inhibitor-free immunosuppression (sirolimus/mycophenolate mofetil)

after heart transplantation: 5-year results. J Heart Lung Transplant 2013;32:277-84.

96. Van Keer J, Derthoo D, Van Caenegem O, et al. The CECARI study: everolimus (Certican®) initiation and calcineurin inhibitor withdrawal in maintenance heart transplant recipients with renal insufficiency: a multicenter, randomized trial. J Transplant 2017;2017:6347138.

97. Guethoff S, Meiser BM, Groetzner J, et al. Ten-year results of a randomized trial comparing tacrolimus versus cyclosporine a in combination with mycophenolate mofetil after heart transplantation. Transplantation 2013;95:629-34.

98. Urbanowicz T, Baszynska-Wachowiak H, Ligowski M, et al. Comparison of conventional tacrolimus versus prolonged release formula as initial therapy in heart transplantation. Ann Transplant 2014;19:295-9.

99. Kobashigawa JA, Renlund DG, Gerosa G, et al. Similar efficacy and safety of enteric-coated mycophenolate sodium (EC-MPS, myfortic) compared with mycophenolate mofetil (MMF) in *de novo* heart transplant recipients: results of a 12-month, single-blind, randomized, parallel-group, multicenter study. J Heart Lung Transplant 2006;25:935-41.

100. Jennings DL, Lange N, Shullo M, et al. Outcomes associated with mammalian target of rapamycin (mTOR) inhibitors in heart transplant recipients: a meta-analysis. Int J Cardiol 2018;265:71-6.

101. Andreassen AK, Andersson B, Gustafsson F, et al. Everolimus initiation and early calcineurin inhibitor withdrawal in heart transplant recipients: a randomized trial. Am J Transplant 2014;14:1828-38.

102. Eisen HJ, Kobashigawa J, Starling RC, et al. Everolimus versus mycophenolate mofetil in heart transplantation: a randomized, multicenter trial. Am J Transplant 2013;13:1203-16.

103. Karia PS, Azzi JR, Heher EC, Hills VM, Schmults CD. Association of sirolimus use with risk for skin cancer in a mixed-organ cohort of solid-organ transplant recipients with a history of cancer. JAMA Dermatol 2016;152:533-40.

104. Euvrard S, Morelon E, Rostaing L, et al. Sirolimus and secondary skin-cancer prevention in kidney transplantation. N Engl J Med 2012;367:329-39.

105. Rivinius R, Helmschrott M, Ruhparwar A, et al. Analysis of malignancies in patients after heart transplantation with subsequent immunosuppressive therapy. Drug Des Devel Ther 2015;9:93-102.

106. Doesch AO, Muller S, Konstandin M, et al. Malignancies after heart transplantation: incidence, risk factors, and effects of calcineurin inhibitor withdrawal. Transplant Proc 2010;42:3694-9.

107. Wang YJ, Chi NH, Chou NK, et al. Malignancy after heart transplantation under everolimus versus mycophenolate mofetil immunosuppression. Transplant Proc 2016;48:969-73.

108. Baraldo M, Gregoraci G, Livi U. Steroid-free and steroid withdrawal protocols in heart transplantation: the review of literature. Transpl Int 2014;27:515-29.

109. Crespo-Leiro MG, Zuckermann A, Bara C, et al. Concordance among pathologists in the second Cardiac Allograft Rejection Gene Expression Observational Study (CARGO II). Transplantation 2012;94:1172-7.

110. Chi NH, Chou NK, Tsao CI, et al. Endomyocardial biopsy in heart transplantation: schedule or event? Transplant Proc 2012;44:894-6.

111. Parkes MD, Aliabadi AZ, Cadeiras M, et al. An integrated molecular diagnostic report for heart transplant biopsies using an ensemble of diagnostic algorithms. J Heart Lung Transplant 2019;38:636-46.

112. Damodaran A, Dardas T, Wu AH, et al. Changes in serial B-type natriuretic peptide level independently predict cardiac allograft rejection. J Heart Lung Transplant 2012;31:708-14.

113. O'Neill JO, McRae AT 3rd, Troughton RW, et al. Brain natriuretic peptide levels do not correlate with acute cellular rejection in *de novo* orthotopic heart transplant recipients. J Heart Lung Transplant 2005;24:416-20.

114. Patel PC, Hill DA, Ayers CR, et al. High-sensitivity cardiac troponin I assay to screen for acute rejection in patients with heart transplant. Circ Heart Fail 2014;7:463-9.

115. Antonczyk K, Niklewski T, Antonczyk R, et al. Speckle-tracking echocardiography for monitoring acute rejection in transplanted heart. Transplant Proc 2018;50:2090-4.

116. Butler CR, Savu A, Bakal JA, et al. Correlation of cardiovascular magnetic resonance imaging findings and endomyocardial biopsy results in patients undergoing screening for heart transplant rejection. J Heart Lung Transplant 2015;34:643-50.

117. Bonnemains L, Cherifi A, Girerd N, Odille F, Felblinger J. Design of the DRAGET study: a multicentre controlled diagnostic study to assess the detection of acute rejection in patients with heart transplant by means of T2 quantification with MRI in comparison to myocardial biopsies. BMJ Open 2015;5:e008963.

118. Crespo-Leiro MG, Stypmann J, Schulz U, et al. Clinical usefulness of gene-expression profile to rule out acute rejection after heart transplantation: CARGO II. Eur Heart J 2016;37:2591-601.

119. Kobashigawa J, Patel J, Azarbal B, et al. Randomized pilot trial of gene expression profiling versus heart biopsy in the first year after heart transplant: early invasive monitoring attenuation through gene expression trial. Circ Heart Fail 2015;8:557-64.

120. De Vlaminck I, Valantine HA, Snyder TM, et al. Circulating cell-free DNA enables noninvasive diagnosis of heart transplant rejection. Sci Transl Med 2014;6:241ra77.

121. Khush KK, Patel J, Pinney S, et al. Non-invasive detection of graft injury after heart transplantation using donor-derived cell-free DNA: a prospective multi-center study. Am J Transplant 2019;19:2889-99.

122. Duong Van Huyen JP, Tible M, Gay A, et al. MicroRNAs as non-invasive biomarkers of heart transplant rejection. Eur Heart J 2014;35:3194-202.

123. Di Francesco A, Fedrigo M, Santovito D, et al. MicroRNA signatures in cardiac biopsies and detection of allograft rejection. J Heart Lung Transplant 2018;37:1329-40.

124. Lund LH, Khush KK, Cherikh WS, et al. The Registry of the International Society for Heart and Lung Transplantation: thirty-fourth adult heart transplantation report-2017; focus theme: allograft ischemic time. J Heart Lung Transplant 2017;36:1037-46.

125. Kobashigawa J, Crespo-Leiro MG, Ensminger SM, et al. Report from a consensus conference on antibody-mediated rejection in heart transplantation. J Heart Lung Transplant 2011;30:252-69.

126. Reed EF, Demetris AJ, Hammond E, et al. Acute antibody-mediated rejection of cardiac transplants. J Heart Lung Transplant 2006;25:153-9.

127. Park MH, Starling RC, Ratliff NB, et al. Oral steroid pulse without taper for the treatment of asymptomatic moderate cardiac allograft rejection. J Heart Lung Transplant 1999;18:1224-7.

128. Bierl C, Miller B, Prak EL, et al. Antibody-mediated rejection in heart transplant recipients: potential efficacy of B-cell depletion and antibody removal. Clin Transpl 2006:489-96.

129. Garrett HE Jr, Duvall-Seaman D, Helsley B, Groshart K. Treatment of vascular rejection with rituximab in cardiac transplantation. J Heart Lung Transplant 2005;24:1337-42.

130. Chih S, Tinckam KJ, Ross HJ. A survey of current practice for antibody-mediated rejection in heart transplantation. Am J Transplant 2013;13:1069-74.

131. Zhang Q, Hickey M, Drogalis-Kim D, et al. Understanding the correlation between DSA, complement activation, and antibody-mediated rejection in heart transplant recipients. Transplantation 2018;102: e431-8.

132. Barten MJ, Schulz U, Beiras-Fernandez A, et al. The clinical impact of donor-specific antibodies in heart transplantation. Transplant Rev (Orlando) 2018;32:207-17.

133. Tambur AR, Campbell P, Claas FH, et al. Sensitization in Transplantation: Assessment of Risk (STAR) 2017 Working Group meeting report. Am J Transplant 2018;18:1604-14.

134. Kobashigawa JA, Tobis JM, Starling RC, et al. Multicenter intravascular ultrasound validation study among heart transplant recipients: outcomes after five years. J Am Coll Cardiol 2005;45:1532-7.

135. Watanabe T, Seguchi O, Yanase M, et al. Donor-transmitted atherosclerosis associated with worsening cardiac allograft vasculopathy after heart transplantation: serial volumetric intravascular ultrasound analysis. Transplantation 2017;101:1310-9.

136. Haddad F, Khazanie P, Deuse T, et al. Clinical and functional correlates of early microvascular dysfunction after heart transplantation. Circ Heart Fail 2012;5:759-68.

137. Yang HM, Khush K, Luikart H, et al. Invasive assessment of coronary physiology predicts late mortality after heart transplantation. Circulation 2016;133:1945-50.

138. Chirakarnjanakorn S, Starling RC, Popovic ZB, Griffin BP, Desai MY. Dobutamine stress echocardiography during follow-up surveillance in heart transplant patients: diagnostic accuracy and predictors of outcomes. J Heart Lung Transplant 2015;34:710-7.

139. Manrique A, Bernard M, Hitzel A, et al. Diagnostic and prognostic value of myocardial perfusion gated SPECT in orthotopic heart transplant recipients. J Nucl Cardiol 2010;17:197-206.

140. Wever-Pinzon O, Romero J, Kelesidis I, et al. Coronary computed tomography angiography for the detection of cardiac allograft vasculopathy: a meta-analysis of prospective trials. J Am Coll Cardiol 2014;63: 1992-2004.

141. Chih S, Chong AY, Erthal F, et al. PET assessment of epicardial intimal disease and microvascular dysfunction in cardiac allograft vasculopathy. J Am Coll Cardiol 2018;71:1444-56.

142. Bravo PE, Bergmark BA, Vita T, et al. Diagnostic and prognostic value of myocardial blood flow quantification as non-invasive indicator of cardiac allograft vasculopathy. Eur Heart J 2018;39:316-23.

143. Kobashigawa JA, Katznelson S, Laks H, et al. Effect of pravastatin on outcomes after cardiac transplantation. N Engl J Med 1995;333:621-7.

144. Kobashigawa JA, Pauly DF, Starling RC, et al. Cardiac allograft vasculopathy by intravascular ultrasound in heart transplant patients: substudy from the everolimus versus mycophenolate mofetil randomized, multicenter trial. JACC Heart Fail 2013;1:389-99.

145. Kim M, Bergmark BA, Zelniker TA, et al. Early aspirin use and the development of cardiac allograft vasculopathy. J Heart Lung Transplant 2018;36:1344-9.

146. Fearon WF, Okada K, Kobashigawa JA, et al. Angiotensin-converting enzyme inhibition early after heart transplantation. J Am Coll Cardiol 2017;69:2832-41.

147. Arora S, Ueland T, Wennerblom B, et al. Effect of everolimus introduction on cardiac allograft vasculopathy–results of a randomized, multicenter trial. Transplantation 2011;92:235-43.

148. Matsuo Y, Cassar A, Yoshino S, et al. Attenuation of cardiac allograft vasculopathy by sirolimus: relationship to time interval after heart transplantation. J Heart Lung Transplant 2013;32:784-91.

149. Dasari TW, Hennebry TA, Hanna EB, Saucedo JF. Drug eluting versus bare metal stents in cardiac allograft vasculopathy: a systematic review of literature. Catheter Cardiovasc Interv 2011;77:962-9.

150. Goldraich LA, Stehlik J, Kucheryavaya AY, Edwards LB, Ross HJ. Retransplant and medical therapy for cardiac allograft vasculopathy: International Society for Heart and Lung Transplantation Registry analysis. Am J Transplant 2015;16:301-9.

151. Youn JC, Stehlik J, Wilk AR, et al. Temporal trends of *de novo* malignancy development after heart transplantation. J Am Coll Cardiol 2018;71:40-9.

152. Garrett GL, Blanc PD, Boscardin J, et al. Incidence of and risk factors for skin cancer in organ transplant recipients in the United States. JAMA Dermatol 2017;153:296-303.

153. Kotton CN, Kumar D, Caliendo AM, et al. The third international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. Transplantation 2018;102:900-31.

154. Higgins RS, Brown RN, Chang PP, et al. A multi-institutional study of malignancies after heart transplantation and a comparison with the general United States population. J Heart Lung Transplant 2014;33: 478-85.

155. Chiu B, Sergi C. Malignancy after heart transplantation: a systematic review of the incidence and risk factors compared with other solid organ transplants. J Clin Exp Cardiolog 2013;1:2-4.

156. O'Reilly Zwald F, Brown M. Skin cancer in solid organ transplant recipients: advances in therapy and management: part II. Management of skin cancer in solid organ transplant recipients. J Am Acad Dermatol 2011;65:263-79.

157. Acuna SA, Huang JW, Scott AL, et al. Cancer screening recommendations for solid organ transplant recipients: a systematic review of clinical practice guidelines. Am J Transplant 2017;17:103-14.

158. Harwood CA, Mesher D, McGregor JM, et al. A surveillance model for skin cancer in organ transplant recipients: a 22-year prospective study in an ethnically diverse population. Am J Transplant 2013;13:119-29.

159. Hayes D Jr, Tumin D, Foraker RE, Tobias JD. Posttransplant lymphoproliferative disease and survival in adult heart transplant recipients. J Cardiol 2017;69:144-8.

160. Al-Mansour Z, Nelson BP, Evens AM. Post-transplant lymphoproliferative disease (PTLD): risk factors, diagnosis, and current treatment strategies. Curr Hematol Malig Rep 2013;8:173-83.

161. Trappe R, Oertel S, Leblond V, et al. Sequential treatment with rituximab followed by CHOP chemotherapy in adult B-cell post-transplant lymphoproliferative disorder (PTLD): the prospective international multicentre phase 2 PTLD-1 trial. Lancet Oncol 2012;13: 196-206.

162. Erdoes LS, Hunter GC, Venerus BJ, et al. Prospective evaluation of peripheral vascular disease in heart transplant recipients. J Vasc Surg 1995;22:434-40 [discussion: 40-2].

163. van de Beek D, Kremers W, Daly RC, et al. Effect of neurologic complications on outcome after heart transplant. Arch Neurol 2008;65:226-31.

164. Cemillan CA, Alonso-Pulpon L, Burgos-Lazaro R, et al. Neurological complications in a series of 205 orthotopic heart transplant patients [in Spanish]. Rev Neurol 2004;38:906-12.

165. Patlolla V, Mogulla V, DeNofrio D, Konstam MA, Krishnamani R. Outcomes in patients with symptomatic cerebrovascular disease undergoing heart transplantation. J Am Coll Cardiol 2011;58:1036-41.

166. Belvis R, Marti-Fabregas J, Cocho D, et al. Cerebrovascular disease as a complication of cardiac transplantation. Cerebrovasc Dis 2005;19:267-71.

167. Alejaldre A, Delgado-Mederos R, Santos MA, Marti-Fabregas J. Cerebrovascular complications after heart transplantation. Curr Cardiol Rev 2010;6:214-7.

168. Silva Enciso J, Kato TS, Jin Z, et al. Effect of peripheral vascular disease on mortality in cardiac transplant recipients (from the United Network of Organ Sharing Database). Am J Cardiol 2014;114:1111-5.

169. Dasari T, Heroux A, Peyton M, Saucedo J. Abdominal aortic aneurysms (AAA) post heart transplantation: a systematic review of literature. Ann Transplant 2011;16:147-52.

170. Wallace ML, Ricco JA, Barrett B. Screening strategies for cardiovascular disease in asymptomatic adults. Prim Care 2014;41:371-97.

171. Cimino FM, Snyder KA. Primary care of the solid organ transplant recipient. Am Fam Physician 2016;93:203-10.

172. Humar A, Lebranchu Y, Vincenti F, et al. The efficacy and safety of 200 days valganciclovir cytomegalovirus prophylaxis in high-risk kidney transplant recipients. Am J Transplant 2010;10:1228-37.

173. Razonable RR, Humar A. Cytomegalovirus in solid organ transplant recipients-Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant 2019;33:e13512.

174. Witzke O, Nitschke M, Bartels M, et al. Valganciclovir prophylaxis versus preemptive therapy in cytomegalovirus-positive renal allograft recipients: long-term results after 7 years of a randomized clinical trial. Transplantation 2018;102:876-82.

175. Reischig T, Hribova P, Jindra P, et al. Long-term outcomes of preemptive valganciclovir compared with valacyclovir prophylaxis for prevention of cytomegalovirus in renal transplantation. J Am Soc Nephrol 2012;23:1588-97.

176. Iriart X, Challan Belval T, Fillaux J, et al. Risk factors of pneumocystis pneumonia in solid organ recipients in the era of the common use of posttransplantation prophylaxis. Am J Transplant 2015;15:190-9.

177. Wang EH, Partovi N, Levy RD, et al. Pneumocystis pneumonia in solid organ transplant recipients: not yet an infection of the past. Transpl Infect Dis 2012;14:519-25.

178. Munoz P, Munoz RM, Palomo J, et al. Pneumocystis carinii infection in heart transplant recipients. Efficacy of a weekend prophylaxis schedule. Medicine (Baltimore) 1997;76:415-22.

179. Stern A, Green H, Paul M, Vidal L, Leibovici L. Prophylaxis for pneumocystis pneumonia (PCP) in non-HIV immunocompromised patients. Cochrane Database Syst Rev 2014;10:CD005590.

180. Havik OE, Sivertsen B, Relbo A, et al. Depressive symptoms and all-cause mortality after heart transplantation. Transplantation 2007;84:97-103.

181. Dew MA, Myaskovsky L, DiMartini AF, et al. Onset, timing and risk for depression and anxiety in family caregivers to heart transplant recipients. Psychol Med 2004;34:1065-82.

182. Favaro A, Gerosa G, Caforio AL, et al. Posttraumatic stress disorder and depression in heart transplantation recipients: the relationship with outcome and adherence to medical treatment. Gen Hosp Psychiatry 2011;33:1-7.

183. Myaskovsky L, Posluszny DM, Schulz R, et al. Predictors and outcomes of health-related quality of life in caregivers of cardiothoracic transplant recipients. Am J Transplant 2012;12:3387-97.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2019.12.025.