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ISHLT GUIDELINE

The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: A 10-year update

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In 2005, the International Society for Heart and Lung Transplantation (ISHLT) Board of Directors commissioned the development of the first International Listing Criteria for Heart Transplantation, published in 2006.[1] Subsequently, the ISHLT commissioned a focused update to concentrate on evolving areas of importance, not fully addressed previously. These include congenital heart disease (CHD), restrictive cardiomyopathy, and infectious diseases. In addition, we undertook a review of all 2006 guidelines to update those where new information was evident or evolution in practice demanded significant changes.

Section I (general considerations): A review and revision of the 2006 guideline

All recommendations from the prior guideline were reviewed and the details of the older and newer versions are comprehensively summarized in Table 1. Specific areas of changes are discussed with the supporting evidence.

Please note that the numeric categorization has been adjusted to coincide with the 2006 guidelines as closely as possible.

1.1. Cardiopulmonary stress testing

The 2006 recommendations for cardiopulmonary stress testing remain unchanged in the 2016 version, with the exception of an additional comment on cardiac resynchronization therapy (CRT) devices.

Recommendation: The presence of a CRT device does not alter the current peak volume of oxygen consumption (Vo_2) cutoff recommendations (Class I, Level of Evidence: B).

Evidence from the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial has shown that despite improvements in New York Heart Association Functional Classification or 6-minute walk test distance, CRT did not have an effect on the predictability of peak Vo_2 on adverse cardiac events.[2] A more recent retrospective study evaluated the predictability of peak Vo_2 in patients undergoing evaluation for heart transplantation (HT) with an implantable cardioverter defibrillator (ICD), CRT, or both (CRT-D) devices. This study suggested that a peak $Vo_2 \leq 10$ ml/kg/min rather than the traditional cutoff value of ≤ 14 ml/kg/min may be more useful for risk stratification in the device era.[3] At this time, we feel that using currently accepted peak Vo_2 values are appropriate when taken into context with the rest of the data collected during the evaluation process.

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Table 1 A Comparison of the 2006 vs 2016 Guidelines for Section I (General Considerations)

2006 Guideline recommendation	2016 Guideline recommendation
1.1. Cardiopulmonary stress testing to guide transplant listing	**1.1. Cardiopulmonary stress testing to guide transplant listing**
A maximal cardiopulmonary exercise test is defined as one with a respiratory exchange ratio (RER) $>$ 1.05 and achievement of an anaerobic threshold on optimal pharmacologic therapy (**Class I, Level of Evidence: B**).	Continuing approval without change.
	The presence of a CRT device does not alter the current peak Vo_2 cutoff recommendations (Class I, Level of Evidence: B).
In patients intolerant of a β-blocker, a cutoff for peak oxygen consumption (Vo_2) of $\leq$ 14 ml/kg/min should be used to guide listing (**Class I, Level of Evidence: B**).	Continuing approval without change.
In the presence of a β-blocker, a cutoff for peak Vo_2 of $\leq$ 12 ml/kg/min should be used to guide listing (**Class I, Level of Evidence: B**).	Continuing approval without change.
In young patients ($<$ 50 years) and women, it is reasonable to consider using alternate standards in conjunction with peak Vo_2 to guide listing, including percent of predicted ($\leq$ 50%) peak Vo_2 (**Class IIa, Level of Evidence: B**).	Continuing approval without change.
In the presence of a sub-maximal cardiopulmonary exercise test (RER $<$ 1.05), use of ventilation equivalent of carbon dioxide (V_E/Vco_2) slope of $>$ 35 as a determinant in listing for transplantation may be considered (**Class IIb, Level of Evidence: C**).	Continuing approval without change.
In obese (body mass index [BMI] $>$ 30 kg/m^2) patients, adjusting peak Vo_2 to lean body mass may be considered. A lean body mass–adjusted peak Vo_2 of $<$ 19 ml/kg/min can serve as an optimal threshold to guide prognosis (**Class IIb, Level of Evidence: B**).	Continuing approval without change.
Listing patients based solely on the criterion of a peak Vo_2 measurement should not be performed (**Class III, Level of Evidence: C**).	Continuing approval without change.
1.2. Use of heart failure prognosis scores	**1.2. Use of heart failure prognosis scores**
In circumstances of ambiguity (e.g., peak $Vo_2 >$ 12 and $<$14 ml/kg/ml) a Heart Failure Survival Score (HFSS) may be considered, and it may add discriminatory value to determining prognosis and guide listing for transplantation for ambulatory patients (**Class IIb, Level of Evidence: C**).	**Heart failure prognosis scores should be performed along with cardiopulmonary exercise test to determine prognosis and guide listing for transplantation for ambulatory patients. An estimated 1-year survival as calculated by the Seattle Heart Failure Model (SHFM) of $<$ 80% or a Heart Failure Survival Score (HFSS) in the high/medium risk range should be considered as reasonable cut points for listing (Class IIb, Level of Evidence: C).** **Listing patients solely on the criteria of heart failure survival prognostic scores should not be performed (Class III, Level of Evidence: C).**
1.3. Role of diagnostic right-heart catheterization	**1.3. Role of diagnostic right-heart catheterization**
Right heart catheterization (RHC) should be performed on all candidates in preparation for listing for cardiac transplantation and annually until transplantation (**Class 1, Level of Evidence: C**).	Right heart catheterization (RHC) should be performed on all **adult** candidates in preparation for listing for cardiac transplantation and **periodically** until transplantation (**Class 1, Level of Evidence: C**). **Periodic RHC is not advocated for routine surveillance in children (Class III, Level of Evidence: C).**
RHC should be performed at 3- to 6-month intervals in listed patients, especially in the presence of reversible pulmonary hypertension or worsening of heart failure symptoms (**Class I, Level of Evidence: C**).	Continuing approval without change.
A vasodilator challenge should be administered when the pulmonary artery systolic pressure is $\geq$ 50 mm Hg and either the transpulmonary gradient is $\geq$ 15 or the pulmonary vascular resistance (PVR) is $>$ 3Wood units while maintaining a systolic arterial blood pressure $>$ 85 mm Hg (**Class I, Level of Evidence: C**).	Continuing approval without change.

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Table 1 (*Continued*)

2006 Guideline recommendation	2016 Guideline recommendation
When an acute vasodilator challenge is unsuccessful, hospitalization with continuous hemodynamic monitoring should be performed, as often the PVR will decline after 24 to 48 hours of treatment consisting of diuretics, inotropes and vasoactive agents such as inhaled nitric oxide (**Class I, Level of Evidence: C**).	Continuing approval without change.
If medical therapy fails to achieve acceptable hemodynamics, and if the left ventricle cannot be effectively unloaded with mechanical adjuncts, including an intra-aortic balloon pump (IABP) and/or left ventricular assist device (LVAD), it is reasonable to conclude that the pulmonary hypertension is irreversible (**Class IIb, Level of Evidence: C**).	If medical therapy fails to achieve acceptable hemodynamics and if the left ventricle cannot be effectively unloaded with mechanical adjuncts, including an intra-aortic balloon pump (IABP) and/or left ventricular assist device (LVAD), it is reasonable to conclude that the pulmonary hypertension is irreversible. **After LVAD, reevaluation of hemodynamics should be done after 3 to 6 months to ascertain reversibility of pulmonary hypertension (Class IIA, Level of Evidence: C**).
1.4. Comorbidities and their implications for heart transplantation listing	**1.4. Comorbidities and their implications for heart transplantation listing**
1.4.1. Age, obesity, and cancer	**1.4.1. Age, obesity, and cancer**
Patients should be considered for cardiac transplantation if they are $\leq$ 70 years of age (**Class I, Level of Evidence: C**).	Continuing approval without change.
Carefully selected patients $>$ 70 years of age may be considered for cardiac transplantation. For centers considering these patients, the use of an alternate-type program (i.e., use of older donors) may be pursued (**Class IIb, Level of Evidence: C**).	Carefully selected patients $>$ 70 years of age may be considered for cardiac transplantation (**Class IIb, Level of Evidence: C**).
Overall, pre-transplant BMI $>$ 30 kg/m^2 or percent ideal body weight (PIBW) $>$ 140% are associated with poor outcome after cardiac transplantation. For obese patients, it is reasonable to recommend weight loss to achieve a BMI of $<$ 30 kg/m^2 or percent BMI of $<$ 140% of target before listing for cardiac transplantation (**Class IIa, Level of Evidence: C**).	Pre-transplant body mass index **(BMI)** $>$ **35 kg/m^2** is associated with a worse outcome after cardiac transplantation. For such obese patients, it is reasonable to recommend weight loss to achieve a BMI of $\leq$ 35 kg/m^2 before listing for cardiac transplantation (**Class IIa, Level of Evidence: C**).
Pre-existing neoplasms are diverse, and many are treatable with excision, radiotherapy, or chemotherapy to induce cure or remission. In these patients needing cardiac transplantation, collaboration with oncology specialists should occur to stratify each patient as to their risk of tumor recurrence. Cardiac transplantation should be considered when tumor recurrence is low based on tumor type, response to therapy, and negative metastatic work-up. The specific amount of time to wait to transplant after neoplasm remission will depend on the aforementioned factors and no arbitrary time period for observation should be used (**Class I, Level of Evidence: C**).	Continuing approval without change.
1.4.2. Diabetes, renal dysfunction, and peripheral vascular disease	**1.4.2. Diabetes, renal dysfunction, and peripheral vascular disease**
Diabetes with end-organ damage other than non-proliferative retinopathy or poor glycemic control (glycosylated hemoglobin [HbA_{1c}] $>$ 7.5%) despite optimal effort is a relative contraindication for transplant (**Class IIa, Level of Evidence: C**).	Diabetes with end-organ damage (other than non-proliferative retinopathy) or persistent poor glycemic control (glycosylated hemoglobin [HbA_{1c}] $>$ 7.5% **or 58 mmol/mol)** despite optimal effort is a relative contraindication for transplant (**Class IIa, Level of Evidence: C).**
Renal function should be assessed using estimated glomerular filtration rate (eGFR) or creatinine clearance under optimal medical therapy. Evidence of abnormal renal function should prompt further investigation, including renal ultrasonography, estimation for proteinuria, and evaluation for renal arterial disease, to exclude intrinsic renal disease. It is reasonable to consider the presence of irreversible renal dysfunction (eGFR $<$ 40 ml/min/1.73 m^2) as a relative contraindication for heart transplantation alone (**Class IIa, Level of Evidence: C**).	Renal function should be assessed using estimated glomerular filtration rate (eGFR) or creatinine clearance under optimal medical therapy. Evidence of abnormal renal function should prompt further investigation, including renal ultrasonography, estimation of proteinuria, and evaluation for renal arterial disease, to exclude intrinsic renal disease. It is reasonable to consider the presence of irreversible renal dysfunction (**eGFR $<$ 30 ml/min/1.73 m^2**) as a relative contraindication for heart transplantation alone (**Class IIa, Level of Evidence: C**).

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Table 1 (*Continued*)

2006 Guideline recommendation	2016 Guideline recommendation
Clinically severe symptomatic cerebrovascular disease, which is not amenable to revascularization, may be considered a contraindication to transplantation. Peripheral vascular disease may be considered as a relative contraindication for transplantation when its presence limits rehabilitation and revascularization is not a viable option (**Class IIb, Level of Evidence: C**).	**Clinically severe symptomatic cerebrovascular disease may be considered a contraindication to transplantation**. Peripheral vascular disease may be considered a relative contraindication for transplantation when its presence limits rehabilitation and revascularization is not a viable option (**Class IIb, Level of Evidence: C**).
	1.4.3. Assessment of frailty
	Assessment of frailty (3 of 5 possible symptoms, including unintentional weight loss of $\geq$10 pounds within the past year, muscle loss, fatigue, slow walking speed, and low levels of physical activity) could be considered when assessing candidacy (Class IIb, Level of Evidence: C).
	1.4.4. Mechanical circulatory support for bridge to candidacy
	Use of mechanical circulatory support should be considered for patients with potentially reversible or treatable comorbidities, such as cancer, obesity, renal failure, tobacco use, and pharmacologically irreversible pulmonary hypertension, with subsequent reevaluation to establish candidacy (Class IIb, Level of Evidence: C).
1.5. Tobacco use, substance abuse, and psychosocial evaluation in candidates	**1.5. Tobacco use, substance abuse, and psychosocial evaluation in candidates**
1.5.1. Tobacco use	**1.5.1. Tobacco use**
Education on the importance of tobacco cessation and reduction in environmental or second-hand exposure should be performed before the transplant and continue throughout the pre- and post-transplant periods (**Class I, Level of Evidence: C**).	Continuing approval without change.
It is reasonable to consider active tobacco smoking as a relative contraindication to transplantation. Active tobacco smoking during the previous 6 months is a risk factor for poor outcomes after transplantation (**Class IIa, Level of Evidence: C**).	Continuing approval without change.
1.5.2. Substance abuse	**1.5.2. Substance abuse**
A structured rehabilitative program may be considered for patients with a recent (24-month) history of alcohol abuse if transplantation is being considered (**Class IIb, Level of Evidence: C**).	Continuing approval without change.
Patients who remain active substance abusers (including alcohol) should not receive heart transplantation (**Class III, Level of Evidence: C**).	Continuing approval without change
1.5.3. Psychosocial evaluation	**1.5.3. Psychosocial evaluation**
Psychosocial assessment should be performed before listing for transplantation. Evaluation should include an assessment of the patient's ability to give informed consent and comply with instruction, including drug therapy, as well as assessment of the support systems in place at home or in the community (**Class I, Level of Evidence: C**).	Continuing approval without change.
Mental retardation or dementia may be regarded as a relative contraindication to transplantation (**Class IIa, Level of Evidence: C**).	**Any patient for whom social supports are deemed insufficient to achieve compliant care in the outpatient setting may be regarded as having a relative contraindication to transplant. The benefit of heart transplantation in patients with severe cognitive-behavioral disabilities or dementia (e.g., self-injurious behavior, inability to ever understand and cooperate with medical care) has not been established, has the potential for harm, and therefore, heart transplantation cannot be recommended for this sub-group of patients (Class IIa, Level of Evidence: C).**

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Table 1 (*Continued*)

2006 Guideline recommendation	2016 Guideline recommendation
Poor compliance with drug regimens is a risk factor for graft rejection and mortality. Patients who have demonstrated an inability to comply with drug therapy on multiple occasions should not receive transplantation (**Class III, Level of Evidence: C**).	Continuing approval without change.
1.6. Guidance for screening grids and serial pre-transplant evaluation	**1.6. Guidance for screening grids and serial pre-transplant evaluation**
See grid in paper.	Continuing approval without change.
1.7. Dynamic listing and new donor allocation algorithms	**1.7. Dynamic listing and new donor allocation algorithms**
Listed patients who are in an outpatient ambulatory non–inotropic-therapy-dependent state should be continually evaluated for maximal pharmacologic and device therapy, including implantable cardioverter defibrillator (ICD) or biventricular pacing, when appropriate. Such patients must be re-evaluated at 3- to 6-month intervals with cardiopulmonary exercise testing to assess their response to therapy and, if they have improved significantly, they may be candidates for delisting (**Class I, Level of Evidence: C**).	Listed patients in an outpatient, ambulatory, non–inotropic therapy–dependent state should be continually evaluated for maximal pharmacologic and device therapy, including implantable cardioverter defibrillator (ICD) or biventricular pacing, when appropriate. Such patients must be re-evaluated at 3- to 6-month intervals with cardiopulmonary exercise testing and **heart failure survival prognostic scores** to assess their response to therapy and, if they have improved significantly, should be considered for delisting (**Class I, Level of Evidence: C**).
Redesigned allocation algorithms should be considered that allow for the prioritization of higher-status patients within larger geographic areas (within accepted safe ischemic time limitations). This practice may reduce deaths on the waiting list by both providing more hearts in a timely fashion to the higher-acuity population (**Class I, Level of Evidence: C**).	**Delete**
	Higher prioritization for highly sensitized patients may be considered due to difficulty obtaining a donor, causing excessive waiting times and an increase in waiting list mortality (Class IIb, Level of Evidence: C).
	1.8 Retransplantation
	Retransplantation is indicated for those patients who develop significant CAV with refractory cardiac allograft dysfunction, without evidence of ongoing rejection (Class IIa, Level of Evidence: C).

1.2. Use of heart failure survival prognosis scores

Heart failure survival scores (HFSSs) have been used to predict morbidity and mortality in ambulatory heart failure patients. Their usefulness in guiding HT listing in ambulatory patients has been evaluated.

Recommendation: Heart failure survival prognosis scores may be assessed along with the cardiopulmonary exercise testing to determine prognosis and guide listing for transplantation for ambulatory patients. An estimated 1-year survival, as calculated by the Seattle Heart Failure Model (SHFM) of $< 80\%$, or an HFSS in the high-risk to medium-risk range should be considered as reasonable cut points for listing (Class IIb, Level of Evidence: C).

The use of risk scores to assist clinicians with therapeutic decisions has increased, especially with the introduction of various risk models for mechanical circulatory support (MCS). The SHFM and HFSS have been evaluated as tools to guide listing for HT.

Notably, the SHFM was found to potentially underestimate 1-year risk of needing urgent transplantation, ventricular assist device (VAD), or mortality in patients with advanced heart failure being considered for transplantation and in some special populations.[4,5] For those patients with intermediate risk of needing urgent transplantation, VAD, or mortality as assessed by the SHFM, the addition of peak Vo_2 may assist in improved risk stratification and aid listing decisions.[6]

The HFSS was compared with peak Vo_2 in a retrospective study of heart failure patients with CRT, CRT-D, or ICD alone.[3] The HFSS outperformed peak VO_2 in its ability to discriminate between patients at low or medium risk of death at 1 year. Goda et al[7] went on to determine that combining both risk scores in patients undergoing transplant evaluation outperformed either risk score alone in predicting event-free survival. These risk scores may assist the clinician in discriminating patients who should be listed for transplantation; however, the inherent limitations of each risk score need to be kept in mind.

Recommendation: Listing patients solely on the criteria of heart failure survival prognostic scores should not be performed (Class III, Level of Evidence: C).

1.3. Role of diagnostic right-heart catheterization

Right-heart catheterization (RHC) remains an important test for assessing and maintaining HT candidacy. The following changes are regarding timing for repeat measurements.

Recommendation: RHC should be performed on all adult candidates in preparation for listing for cardiac transplantation and periodically until transplantation (Class I, Level of Evidence: C). Periodic RHC is not advocated for routine surveillance in children (Class III, Level of Evidence: C).

There was consensus that RHC should be performed periodically as the medical team feels it is indicated and that annual evaluation may be too long of a time period in some patients. In the previous guideline, a time period frequency of 3 to 6 months was suggested; however, at this time, we believe that programs should individualize the frequency depending on the situation (presence of pulmonary hypertension on the initial RHC, ongoing stability of heart failure, current left ventricular assist device [LVAD] support). RHC will need to be considered case-by-case in children, and routine periodic surveillance is not generally advocated, unless evidence for clinical change is noted.

Recommendation: If medical therapy fails to achieve acceptable hemodynamics and if the LV cannot be effectively unloaded with mechanical adjuncts, including an intra-aortic balloon pump (IABP) and/or LVAD, it is reasonable to conclude that the pulmonary hypertension is irreversible. After LVAD implantation, re-evaluation of hemodynamics should be done after 3 to 6 months to ascertain reversibility of pulmonary hypertension (Class IIA, Level of Evidence: C).

Elevated pulmonary vascular resistance (PVR) that is refractory to medical therapy may be a contraindication to HT, depending on severity. VADs have been used in patients with refractory elevations in PVR. Investigators in 2 separate studies have shown that this strategy can be successful at reducing PVR into a range that is safe for cardiac transplantation.[8,9] More importantly, both groups of authors reported some benefit as early as 1 month, but it may take as long as 3 to 6 months to achieve maximum reversibility. Therefore, in order to make full determination of reversibility after VAD implantation, it is important to allow enough time for this therapy to have an effect.

1.4. Comorbidities and their implications for HT listing

Evaluation and handling of comorbidities is imperative in order to improve post-transplant outcomes. In this section, the issues of age, obesity, and renal function were modified according to contemporary practice. The use of MCS systems in patients with comorbidities and their implications were also discussed in this guideline.

1.4.1(a) Age

Recommendation: Carefully selected patients >70 years of age may be considered for cardiac transplantation (Class IIb, Level of Evidence: C).

Goldstein et al[10] reported the outcomes of cardiac transplantation in septuagenarians who were carefully evaluated and underwent HT in the United States. These patients derived benefit from this therapy, suffering less rejection but a higher mortality than those slightly younger. Most programs that are performing transplantation in patients aged >70 years are doing so with both specific donor and recipient criteria in place. Therefore, the need to state use of an "alternative allocation" program was felt to be unnecessary and adds to confusion. Nevertheless, local policies to define the upper age limit for eligibility to transplant should be placed into the context of local organ availability and quality in order to maintain acceptable transplant outcomes and a reasonable chance to transplant all listed patients.

1.4.1 (b) Obesity

Recommendation: A pre-transplant body mass index (BMI) >35 kg/m^2 is associated with a worse outcome after cardiac transplantation. For such obese patients, it is reasonable to recommend weight loss to achieve a BMI of ≤35 kg/m^2 before listing for cardiac transplantation (Class IIa, Level of Evidence: C).

Several reports have been published since the 2006 guidelines regarding the effect of BMI on outcomes after HT.[11–13] BMI in the obese range but < 35 kg/m^2 has not been convincingly associated with an increase in mortality after transplantation. However, those patients with a BMI >35 kg/m^2 had longer waiting times, were less likely to find a suitable donor, and in some reports had an increase in post-transplant morbidity and mortality. On the basis of these data, the guideline has been amended to recommend that patients achieve a BMI ≤ 35 kg/m^2 for listing. Because BMI is the parameter used most often, we opted to remove percentage ideal body weight < 140% from the guideline.

1.4.2 (a) Diabetes mellitus

Recommendation: Diabetes with end-organ damage (other than non-proliferative retinopathy) or persistent poor glycemic control (glycosylated hemoglobin [HbA$_{1c}$] > 7.5% or 58 mmol/mol), despite optimal effort, is a relative contraindication for transplant (Class IIa, Level of Evidence: C).

The addition of a HbA$_{1c}$ value of 58 mmol/mol was added to be comprehensive and internationally relevant.

1.4.2 (b) Renal function

Recommendation: Renal function should be assessed using the estimated glomerular filtration rate (eGFR) or creatinine clearance under optimal medical therapy. Evidence of abnormal renal function should prompt further investigation, including renal ultrasonography, estimation of proteinuria, and evaluation for renal arterial disease, to exclude intrinsic renal disease. It is reasonable to consider the presence of irreversible renal dysfunction (eGFR < 30 ml/min/1.73 m^2) as a relative

contraindication for HT alone (Class IIa, Level of Evidence: C).

Renal dysfunction continues to play an important role in outcomes after HT. More often than not, committees are forced to make decisions regarding HT alone, heart-kidney transplant, or deferring transplantation altogether. Unfortunately, which test or formula required to determine irreversible renal dysfunction has not been fully elucidated, with several prevalent formulas to measure eGFR. In the current guidelines, the eGFR, a measure of renal function, was reduced to < 30 ml/min/1.73 m^2 to be considered as a relative contraindication for HT.

1.4.2 (c) Cerebral and peripheral vascular disease

Recommendation: Clinically severe symptomatic cerebrovascular disease (CVD) may be considered a contraindication to transplantation. Peripheral vascular disease may be considered a relative contraindication for transplantation when its presence limits rehabilitation and revascularization is not a viable option (Class IIb, Level of Evidence: C).

Cerebrovascular accidents are a devastating complication after transplant surgery and can greatly alter quality of life and survival. The prior guideline included "not amenable to revascularization" in its statement; however, in review of the data, we cannot be certain whether the post-transplant risk can indeed be modified that in patients with a prior cerebrovascular event. Patlolla et al[14] examined 1,078 patients from an existing registry and found that patients with symptomatic CVD are at an increased risk of stroke and functional decline after transplantation independent of other variables, but not death, during long-term follow-up. This study suffers from the potential for misclassification, and indeed, some patients may have undergone revascularization, which could have modified their risk but it remains unknown. Because of this particular uncertainty, the statement regarding CVD was amended. Recommendations regarding peripheral vascular disease remain unchanged.

1.4.3 Assessment of frailty

The role of frailty in heart failure has recently been investigated and warrants discussion, especially as we move to consider older patients for cardiac transplantation.

Recommendation: Assessment of frailty (3 of 5 possible symptoms, including unintentional weight loss of $\geq$10 pounds within the past year, muscle loss, fatigue, slow walking speed, and low levels of physical activity) could be considered when assessing candidacy (Class IIb, Level of Evidence: C).

Frailty is a clinically identifiable disorder of amplified vulnerability of age-related decline in reserve and function across multiple physiologic systems brought on with minor stressors.[15,16] Not all elderly patients are frail, but those who meet the definition are likely to have at least 3 of 5 possible symptoms, including unintentional weight loss ($\geq$10 pounds within the past year), muscle loss, fatigue, slow walking speed, and low levels of physical activity. The presence of frailty increases heart failure resource use.[16] Candidates for LVAD implantation have been noted to segregate outcomes adversely in those diagnosed with frailty.[17]

There are several concerns with requiring a measure of frailty as criteria for HT listing. Several different assessment tools, from testing of grip strength or gait speed to questionnaires, or a combination of both, have been studied.[18–21] Some methods may be time consuming and difficult to perform, whereas other measures, such as slower gait speed, are easy to apply. However, the lack of standardization makes using frailty as definitive criteria for listing difficult.

Other noteworthy concerns regarding frailty were discussed in the context of heart failure and VAD candidates by Flint et al.[22] This group draws attention to the possibility of frailty that may be responsive to advanced therapy, such as an LVAD, vs frailty that would be non-responsive to such maneuvers. Therefore, we are unable to assign a higher level of recommendation to this evolving metric at this time.

1.4.4 MCS for bridge to candidacy

Recommendation: Use of MCS should be considered for patients with potentially reversible or treatable comorbidities, such as cancer, obesity, renal failure, tobacco use, and pharmacologically irreversible pulmonary hypertension, with subsequent re-evaluation to establish candidacy (Class IIb, Level of Evidence: C).

MCS as a bridge to candidacy has been used for many of the above-mentioned comorbidities. In situations of pulmonary hypertension, adjunctive therapy with pharmacologic agents, such as sildenafil or milrinone, may be used but the data are too weak to provide a recommendation. Patients failing optimum heart failure therapy, yet requiring more time from their primary cancer before being considered a transplant candidate, might benefit from MCS. Obese patients have been bridged with MCS, but often, the device alone will not suffice to reach the goal of weight loss. The newer continuous-flow devices are associated with no weight loss or potentially weight gain when implanted alone.[23,24] Although these patients can undergo the surgery, they experience more infectious complications and need for repeat surgery than do non-obese patients. Some programs are coupling MCS with weight loss surgeries in order to achieve the desired amount of weight loss needed.[25]

The application of MCS to improve renal dysfunction has met with mixed results. In some cases, renal function improves, including patients who may require temporary renal replacement therapy or dialysis after implantation.[26,27] Those patients with improved renal function after VAD support generally maintain renal function after HT. However, a large percentage of patients with severe renal dysfunction at the time of implantation or after the surgery

have a significant increase in morbidity and mortality. Most of these patients do not survive to transplantation and have as high as a 3-fold increase in mortality.[28]

1.5 Tobacco use, substance abuse, and psychosocial evaluation in candidate

1.5.3 Psychosocial evaluation

Recommendation: Any patient for whom social supports are deemed insufficient to achieve compliant care in the outpatient setting may be regarded as having a relative contraindication to transplant. The benefit of HT in patients with severe cognitive-behavioral disabilities or dementia (e.g., self-injurious behavior, inability to ever understand and cooperate with medical care) has not been established, has the potential for harm, and therefore, HT cannot be recommended for this subgroup of patients (Class IIa, Level of Evidence: C).

The suggested revision places importance on being able to achieve adequate compliance and adherence with the comprehensive plan for medical management after transplantation rather than a focus on purely the intellectual status. It has been argued that patients with intellectual disability who have adequate social support may be deemed reasonable transplant candidates provided there are not any other contraindications after the full candidate evaluation.[29] Although the literature is unclear with respect to the perils of HT in patients with dementia, we believe that transplantation in such a manifest setting has the potential for harm, such that effective medical care may not reasonably and safely be provided.

1.6 Guidance for screening grids and serial pre-transplant evaluation

No changes were made to this grid; however, each program will likely need to update its protocol grids based on the new general and special considerations.

1.7 Dynamic listing and new donor allocation algorithms

Recommendation: Listed patients in an outpatient, ambulatory, non–inotropic therapy–dependent state should be continually evaluated for maximal pharmacologic and device therapy (including ICD or biventricular pacing, when appropriate). Such patients should be re-evaluated at 3- to 6-month intervals with cardiopulmonary exercise testing and heart failure survival prognostic scores to assess their response to therapy and, if they have improved significantly, should be considered for delisting (Class I, Level of Evidence: C).

The new role for heart failure prognostic scores in the initial evaluation also applies to dynamic listing; therefore, the prognostic score assessment was added to the dynamic listing recommendation. Retransplantation and prioritization listing for sensitized patients were 2 areas not mentioned in the 2006 guideline and certainly warrant addition. However, the need to mention blanket allocation algorithms for prioritization was felt unnecessary, and therefore, the guideline pertaining to that aspect was deleted.

Recommendation: Higher prioritization for highly sensitized patients may be considered due to difficulty obtaining a donor causing excessive waiting times and an increase in waiting list mortality (Class IIb, Level of Evidence: C).

Pre-transplant sensitization has been an ongoing issue in cardiac transplantation. The most recent ISHLT registry report showed that 13.8% of HT recipients have an elevated panel-reactive antibody (PRA) test defined as $> 10\%$.[30] Published reports consistently support the association of elevations in circulating antibodies with an increase in mortality, rejection, and the development of cardiac allograft vasculopathy (CAV) in the post-transplant period, as well as longer waiting times and risk of mortality in the pre-transplant phase.[31] Typically, these patients are more likely to be women, have a VAD, received blood transfusions, or had previous surgeries, some of which involve material that led to an increase in antibody productions such as congenital heart surgeries.[32–35]

In 2010, the Canadian Cardiac Transplant Network addressed the concern of longer waiting time for sensitized patients by developing prioritization category 4S for those patients with an elevated calculated PRA (cPRA) $> 80\%$ or a cPRA $> 20\%$ with 3 failed attempts at obtaining a suitable donor due to a positive virtual cross-match.[36] The Canadian Cardiac Transplant Network has since modified the 4S category to include only those patients with a cPRA $> 80\%$, standardized the calculation of cPRA, defined unacceptable antigens, and removed the potential to use the 4S listing criteria for programs that will upfront accept donors despite a positive virtual cross-match.

Kfoury and Kobashigawa[37] have raised several concerns regarding this strategy in an editorial. Central to these issues are the method of determining unacceptable antibodies and the lack of use of antibody titers, the plaguing issue of determining what the presence of pre-formed antibodies really signify, and finally, the notion of desensitization including utility, what method, and for how long. In a 2009 consensus on sensitization before transplantation, it was agreed that quantitative determination of circulating antibodies should be performed in concert with a cPRA.[31]

Although further debate continues on the appropriate way to detect and ultimately address unacceptable antibodies in pre-transplant candidates, methods to reduce waiting times in sicker patients who cannot undergo bridging therapies, such as MCS, may be helpful in bringing these patients to transplantation. In the United States, an exception policy may be used to improve the listing status of a sensitized patient. In this regard, such exceptions apply to potential donors within an organ procurement organization (OPO) and must be agreed upon by both the OPO and the other transplant centers within the OPO (not region wide).

This is a complicated issue, and it is important that allocation systems across various regions be evaluated to provide for prioritization of highly sensitized HT candidates. Importantly, definitions of sensitization need to be standardized across programs to make interpretation of these systems meaningful.

1.8 Retransplantation

Recommendation: Retransplantation is indicated for those patients who develop significant CAV with refractory cardiac allograft dysfunction, without evidence of ongoing acute rejection (Class IIa, Level of Evidence: C).

Heart retransplantation remains a small portion of overall adult transplants performed, accounting for approximately 3% of all transplants.[30] Although outcomes have improved in recent eras,[30] retransplantation remains in the highest 1-year mortality group and is also a significant predictor of long-term mortality. More striking is the finding that the mortality for retransplantation in registry data is 18% at 30 days and 22% at 90 days.[38,39] Even in pediatric patients, retransplantation confers a worse long-term mortality compared with that of primary HTs (63%, 46%, and 26% vs 72%, 60%, and 42% for 5, 10, and 20 years, respectively; $p < 0.001$).[40]

In 2007, Johnson et al[41] published a consensus on indications for retransplantation. It was felt that based on the available data, the development of chronic severe CAV with symptoms of ischemia or heart failure, CAV without symptoms but with moderate to severe LV dysfunction, or symptomatic graft dysfunction without evidence of active rejection are the appropriate indications for retransplantation. Concern was raised that retransplantation within the first 6 months, particularly with immunologic complications as a primary cause, was fraught with high risk. Other series have confirmed this early high risk.[42,43]

A note on HT in children:

Although nearly half of all HTs in children are done for CHD (covered in Section IV), it should be noted that general considerations vary for more traditional indications, such as idiopathic dilated cardiomyopathy, for transplantation in the pediatric population. As an example, RHC is not routinely advocated in children, and many centers use echocardiography-derived hemodynamic parameters. HFFSs have not been validated in children and are not therefore applicable; similarly, certain MCS support, such as the IABP device, are not used. Thus, as these guidelines are translated to the younger patient, such prudence will need to be exercised.

Section II (special considerations): Restrictive and infiltrative cardiomyopathy

A small but substantial proportion of patients with advanced heart failure are affected by diseases expressing a phenotype not characterized by LV dilation and hypokinesis and are usually unresponsive to traditional pharmacologic and device therapy. These diseases include hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathies (RCM), arrhythmogenic right ventricle dysplasia/cardiomyopathy (ARVD/C), and infiltrative cardiomyopathies.[44] The latter group includes patients with cardiac amyloidosis, in whom recently developed disease-specific therapies may address the progression of systemic manifestations of the disease. Prognosis, therapeutic strategies, and indications for HT in these patients require specific considerations and recommendations that will be addressed in this section.

2.1. Restrictive cardiomyopathies

Recommendations: 2.1.1: RCM patients with severe heart failure symptoms (New York Heart Association Functional Classification III–IV) should be referred for HT evaluation (Class I, Level of Evidence: B).

2.1.2: RCM patients evaluated for HT should undergo a complete diagnostic workup to elucidate etiology (infiltrative forms vs idiopathic) and to exclude constrictive pericarditis (Class I, Level of Evidence: C).

2.1.3: The decision to list a RCM patient on the cardiac transplant waiting list should take into consideration specific prognostic indicators (the presence and degree of LV systolic dysfunction, atrial enlargement, pulmonary hypertension, and a low cardiac output) (Class I, Level of Evidence: B).

2.1.4: In RCM, efficacy and safety of LVAD as a bridge to transplant cannot be recommended as standard procedure. MCS with an LVAD or a total artificial heart may be considered in highly selected cases and at experienced centers (Class IIb, Level of Evidence: C).

RCM is a myocardial disease characterized by increased stiffness of the ventricles leading to impaired diastolic filling, often associated with preserved or mildly depressed systolic function, biatrial enlargement, and non-dilated ventricles.[44] This functional and morphologic pattern can be associated with a large spectrum of non-myocardial pathologies, including hypertension, coronary artery disease, and pericardial disease, all of which should be excluded during the diagnostic workup before considering these patients for HT. In this section, we focus on patients affected by infiltrative cardiomyopathies, including amyloidosis; storage diseases, such as Anderson-Fabry disease, hemochromatosis, and glycogenosis; inflammatory myocardial and endomyocardial diseases such as sarcoidosis; and idiopathic RCM, all of which impair myocardial diastolic function. Although a minority among all HT recipients, the proportion of patients with RCM receiving HT has steadily increased, from 0.7% in the early 1990s to 2.2% in the early 2000s.[45]

As opposed to heart failure secondary to DCM, no medical or device therapy has proven to improve outcome in patients with RCM. In addition, symptomatic therapy is often poorly effective because RCM patients are prone to digoxin toxicity, hypotension occurs frequently with vasodilators, and diuretic medications often result in prerenal azotemia due to the steep LV diastolic pressure-volume relationship.[46] Because of these features, HT may be the sole therapeutic option available to improve prognosis in

patients with RCM. Observations from pediatric registries show that the diagnosis of RCM is associated with worse survival and higher need for transplant than DCM or HCM.[47] In other registry series, RCM HT recipients had survival rates at 1, 5, and 10 years similar to those of non-RCM patients, except in sub-groups of those with amyloid heart disease and RCM due to radiation therapy.[45]

Etiology. A thorough diagnostic workup in patients with RCM evaluated for HT is mandatory, because specific etiologies may not only be associated with a sub-optimal risk/benefit ratio of HT but also may mandate alternative therapies or identify relative or absolute contraindications to HT. Besides patients with amyloidosis, who need specific approaches detailed below, RCM etiologic investigation may identify patients benefiting from targeted therapies (e.g., enzyme-replacement drugs in Anderson-Fabry disease[48] and immunosuppressive therapies in sarcoidosis and endomyocardial fibrosis), or with possible systemic involvement that might alter post-transplant outcomes (i.e., glycogen storage diseases). Identification of patients with pericardial constriction, in whom pericardiectomy should be considered, is also important in the pre-transplant evaluation.[49,50] Systemic diseases with a predominant heart involvement may be considered for HT, bearing in mind that specific surveillance for non-cardiac injury progression and post-transplant strategies to treat the underlying disease must be planned (typical examples for this scenario are amyloid light-chain [AL] amyloidosis, and sarcoidosis).

Among the secondary forms of RCM phenotypes, myocardial iron overload, due to familial hemochromatosis or thalassemia major, has been reported as a sporadic indication for HT with acceptable results. [51] Of note, in cases of liver involvement, combined heart-liver transplantation should be considered.[52] Contemporary therapy with iron chelators effectively reduces organ iron deposits and, hopefully, can reduce the need for transplantation in hemochromatosis. It is important to maintain iron-reduction therapy in patients who received a transplant for hemochromatosis because failure to do so can lead to post-transplant recurrent iron deposition.[53]

Prognostic stratification. Although currently available evidence does not allow a risk stratification scheme, in Table 2 we provide a list of typical RCM features associated with an adverse prognosis. Among these, reactive pulmonary hypertension represents a common finding not only associated with a worse pre-transplant prognosis[47,54] but also identifying a high risk for early graft failure and adverse post-transplant outcome. Elevated PVR, often characterized by a low transpulmonary gradient and a low cardiac output, is triggered by the typical RCM feature of chronically elevated ventricular filling pressures. This vasoconstriction may lead to pulmonary vascular remodeling and fixed pulmonary hypertension that will contraindicate HT. Because of this, some pediatric centers consider the development of pulmonary hypertension an indication for listing, regardless of heart failure symptoms, to preempt the onset of irreversible pulmonary vasoconstriction, whereas others point to the importance of pulmonary hypertension in determining survival.[55,56] Regular assessment of right heart hemodynamics, with aggressive use of pulmonary vasodilators (e.g., intravenous nitrates or inhaled nitric oxide), including those with inotropic effects (e.g., milrinone), should be performed in patients on the waiting list to identify the development of irreversible pulmonary vasoconstriction.[55,56] Owing to long-standing right heart failure, a closer evaluation for liver abnormalities, particularly advanced hepatic fibrosis and cirrhosis, may be useful. RCM patients with limited hepatic reserve, evidenced by persistent hepatic dysfunction despite relief from congestion, should be considered for liver biopsy, because the extent of fibrosis or the presence of cirrhosis may be of help in post-transplant risk prognostication, in a manner similar to that for CHD, especially those with a Fontan circulation (discussed in Section IV).

Mechanical circulatory support. Continuous-flow implantable LVADs have largely been tested in patients with dilated LVs and are currently not indicated in patients with RCM or HCM. One center described the use of LVAD implant in 4 patients with RCM and 4 with HCM.[57] The use of LVAD implant is technically challenging, cannot be recommended as standard procedure in RCM patients, and should be used only in selected cases by experienced large-volume centers. Total artificial heart, or paracorporeal or intracorporeal biventricular support, may represent an alternate option for MCS bridging in highly selected RCM patients at experienced centers. The absence of robust data supporting the safety of routine implantable mechanical devices in these patients further underscores the need for timely referral, listing, and prioritization for RCM patients as candidates for HT.

Table 2 Poor Prognostic Markers for Survival in Restrictive Cardiomyopathy[a]

Pulmonary congestion at diagnosis
Angina or ischemic electrocardiographic findings
Left atrial dimension > 60 mm
Male gender
Reactive pulmonary hypertension
Reduced left ventricle fractional shortening
Increased end-diastolic posterior wall thickness

[a]Adapted from Webber et al,[47] Ammash et al,[54] and Murtuza et al.[55]

2.2. Cardiac amyloidosis

Recommendations: 2.2.1 Selected patients with HF due to AL amyloidosis who are not candidates for disease-specific therapies due to cardiovascular compromise may be considered for HT in experienced centers with established collaborations between cardiovascular and hematology teams. Autologous stem cells transplantation (ASCT) should be planned as soon as clinically feasible after recovery from HT (Class IIA, Level of Evidence: B).

2.2.2 Patients with transthyretin related (TTR) amyloidosis involving the heart may be considered for HT.

Familial TTR cardiac amyloidosis patients should be considered for combined heart and liver transplantation in experienced centers with established collaboration between cardiology, hepatology, and neurology teams (Class IIA, Level of Evidence: B).

2.2.3 Amyloid involvement of extracardiac organs must be carefully evaluated when considering AL amyloid patients for sequential HT/ASCT (AL patients) or TTR amyloid patients for HT or combined HT with liver transplantation. Severe extracardiac amyloid organ dysfunction should be considered a contraindication to proceeding with HT (Class IIA, Level of Evidence: B).

Amyloidoses are a family of diseases induced by misfolded or misassembled proteins accumulating in the extracellular matrix of several organ systems. Several types of amyloid can infiltrate the heart, leading to a RCM phenotype, with progressive diastolic and systolic dysfunction, heart failure, and death. Treatment strategies, including HT or combined with simultaneous liver transplant or with subsequent ASCT, depend on the amyloid sub-type and the degree of cardiac and systemic involvement. Accurate diagnosis and classification of amyloid sub-type is essential. The 2 most common subtypes of amyloid that infiltrate the heart are: (1) immunoglobulin AL amyloid—deriving from an indolent clone of plasma cells, and (2) TTR amyloid. TTR amyloidoses comprise 2 kinds of disease: familial disease deriving from misfolding of a mutated TTR, and a non-genetic disease caused by misaggregation of wild-type transthyretin (senile systemic amyloidosis [SSA]). TTR is a transporter protein synthesized by the liver, which has traditionally been the initial target for a transplantation strategy in patients with systemic familial TTR. Much more rarely, other precursor proteins, such as apolipoprotein A1, can cause cardiac amyloidosis.[58,59]

Prognostic stratification. Predicting the survival of cardiac amyloid patients from the time of wait listing to the availability of a donor heart represents a significant challenge, because the number of patients are few and their clinical phenotype at the time of wait listing varies. It appears that the waiting list mortality for cardiac amyloidosis as a primary etiology may be 3-fold higher than that noted for patients with an idiopathic DCM. However, a clear difference between AL and TTR has been suggested. Rapezzi et al[59] showed that AL amyloid patients have a significantly worse survival at 2 years (63%) compared with mutated TTR (98%) and 100% survival for wild-type TTR. Unlike AL amyloidosis, TTR cardiomyopathy is slowly progressive and clinically well tolerated, until marked ventricular wall thickening, diastolic dysfunction, and conduction disease have occurred. More specifically, AL amyloid patients on a waiting list for HT with ASCT strategy showed 35% to 42% death rate.[60]

Overall, once amyloid patients become symptomatic, disease progression is rapid and malignant and results in cardiac-related death. Prognostic stratification has been clearly described in AL patients in pivotal studies from the Mayo Clinic group, defining stage I to III of cardiac involvement based on levels of brain natriuretic peptide (BNP) and of troponin T.[61] More recently, Wechalekar et al[62] further stratified stage III patients based on BNP and systolic blood pressure (Table 3). Although not definitive, these biomarkers may guide referral for HT strategies in AL patients, whereas few data support their utility in TTR patients.[63] Part of the problem in trying to predict outcome for patients affected by cardiac TTR amyloid is the highly variable clinical presentation. In addition to the typical RCM features, cardiovascular prognosis in TTR patients depends on the fibril type (wild-type vs mutated), specific mutation, age of onset, and fragmented vs full-length fibrils.[63] The idea that TTR amyloidosis behaves in an indolent fashion compared with cardiac AL amyloidosis has recently been challenged by the current description of the V122I mutation.[64] This group of patients was found with a disproportionate risk of cardiac death compared with other TTR genotypes: during a 16-month period, the mortality for subjects with this mutation was 73% compared with 22% ($p = 0.03$) for subjects with the wild-type TTR. In addition, the V122I mutation was associated with a greater degree of cardiac involvement and hospitalizations.

Table 3 Criteria for Prognostic Stratification of Cardiac Involvement in Amyloid Light-Chain Amyloidosis[a]

Stages	Criteria
Stage I	NT-pro BNP < 332 ng/L **and** troponin T < 0.035 μg/L
Stage II	NT-pro BNP > 332 ng/L **or** troponin T > 0.035 μg/L
Stage III	NT-pro BNP > 332 ng/L **and** troponin T > 0.035 μg/L
Low risk stage III	NT-pro BNP 332 to 8,500 ng/L **and** SBP > 100 mm Hg
Intermediate risk stage III	NT-pro BNP > 8,500 ng/L **or** SBP < 100 mm Hg
High risk stage III	NT-pro BNP > 8500 ng/L **and** SBP < 100 mm Hg

NT-pro BNP, N-terminal prohormone brain natriuretic peptide; SBP, systolic blood pressure.

[a]Adapted from Dispenzieri et al[61] and Wechalekar et al.[62]

Evaluation for HT. Retrospective analyses and small prospective series have demonstrated the prognostic influence of organ involvement in AL amyloid patients receiving ASCT.[65–67] Important systems that must be thoroughly assessed for amyloid involvement include the gastrointestinal organs (stomach, intestines, liver), the kidneys, the autonomic nervous system, the lungs and pleura, and the coagulation system. The presence of localized amyloid in the skin, bladder and ureters, larynx, or conjunctiva is usually of less effect to the decision regarding suitability for transplantation. The assessment of amyloid involvement in potential HT/ASCT recipients must include both an evaluation of the anatomic extent of light-chain infiltration and the functional effect of the light-chain protein on organ function. Table 4 reviews organ-specific testing for AL amyloid patients to be considered in addition to the usual studies performed to evaluate cardiac transplant candidates. The extent of a patient's hemodynamic compromise must be

Table 4 Evaluation of Extracardiac Organ Amyloid Light-Chain Amyloid Involvement

Organ system	Screening tests
Pulmonary	• Pulmonary function testing, including arterial oximetry, diffusion capacity • Chest X-ray imaging and computed tomography to assess for interstitial disease, effusions • Thoracentesis may be necessary to differentiate manifestations of amyloidosis from heart failure
Gastrointestinal	• Nutritional assessment, including plasma pre-albumin, albumin • Assessment for bleeding by esophagogastroduodenoscopy, colonoscopy • Assessment of amyloid deposition by random biopsy • Assessment of intestinal motility with gastric-emptying studies
Hepatic	• Serum alkaline phosphatase, bilirubin • An alkaline phosphatase $>$ 1.5$\times$ upper limit of normal in the absence of congestion should prompt liver biopsy to assess for portal and parenchymal amyloid deposition. The presence of solitary vascular deposition should not be considered a contraindication to HT/ASCT
Renal	• Measured creatinine clearance or eGFR • 24-hour urinary protein excretion A eGFR or measured creatinine clearance $<$ 50 ml/min/1.73 m^2 in the absence of decompensated heart failure or urinary protein excretion $>$0.5 g/24 hours should prompt renal biopsy to assess the renal amyloid burden
Coagulation	• Factor X and thrombin time Patients with a severe ($<$25%) factor X functional deficiency have $<$ 50% survival after ASCT

ASCT, autologous stem cells transplantation; eGFR, estimated glomerular filtration rate; HT, heart transplantation.

considered in the functional effect of amyloidosis on several of these organs. It may be necessary to optimize a patient's hemodynamics, at times with the use of invasive hemodynamic measurements, to accurately assess the relative contributions of amyloid infiltration and heart failure to a patient's extracardiac organ dysfunction.

In addition, special consideration of the effect of HT, both peri-operatively and the post-operative need for immunosuppression, must be considered in assessing a patient's candidacy. For example, although patients with a creatinine clearance of $<$30 ml/min/1.73 m^2 may be considered adequate for ASCT, the effects of calcineurin inhibitors, necessary after HT, suggest the need for further renal evaluation as outlined in Table 4. The group from Stanford has also published their protocol in a limited group of patients with amyloid heart disease.[68]

In general, patients with cardiac amyloidosis related to multiple myeloma are excluded from consideration for HT/ASCT, because their prognosis after ASCT is not as good as those with primary amyloidosis. In the evaluation of a cardiac amyloid patient for HT/ASCT, assessment for markers of myeloma such as hypercalcemia, a bone marrow aspirate differential of $>$30% plasma cells, and the presence of lytic lesions on bone survey should be undertaken. The performance of HT/ASCT in patients in whom the diagnosis of multiple myeloma is made solely on the bone marrow aspirate differential is controversial at this time.

Transplantation strategy in AL amyloidosis. The dismal initial outcomes of HT *alone* in cardiac AL amyloidosis patients changed with the development of ASCT for the treatment of AL amyloidosis. Dispenzari et al[69] and Skinner et al[70] demonstrated that ASCT, in appropriate candidates, resulted in a median survival of approximately 5 years. These selected successes, as well as the recognition of the limitations of ASCT alone in patients with cardiac involvement, has led to the use of serial HT and ASCT in selected patients for whom heart failure is the major manifestation of their amyloid disease. It was anticipated that AL cardiac amyloid patients undergoing HT would have an excellent prognosis after ASCT, similar to that in patients initially without cardiac involvement. In small series, long-term (5-year) survival with this highly selected approach is approximately 60%. The most common cause of death after HT/ASCT was the recurrence of light-chain production and end-organ disease and dysfunction, including cardiac recurrence.[71–73]

There are several considerations regarding the timing of ASCT after HT. The cessation of light-chain production is essential to prevent the progression of extracardiac organ dysfunction, favoring ASCT early after HT. The intense immunosuppression occurring during induction therapy for ASCT suggests that a patient's background immunosuppression be relatively low before ASCT to minimize the risk of infection. Thus, ASCT is delayed for 6 to 8 months after HT in reported series. Novel treatment algorithms, including the combination of cytotoxic drugs with proteosome inhibitors and immunomodulatory agents, may come to represent definitive therapy for AL amyloidosis in selected patients and is less toxic than ASCT.[74]

Transplant strategy in TTR amyloidosis. The variant TTR protein deposited in multiple organs in TTR amyloid is produced primarily in the liver. Liver transplantation undertaken for TTR amyloid prevents production of most of this protein and effectively halts progression of the systemic manifestations in most patients. In particular, patients with the Va130Met-related ATTR, in whom neurologic symptoms are prominent, have significant improvement in systemic manifestations.[75] HT can therefore be used to treat the heart failure manifestations of TTR amyloid in appropriate transplant candidates. Combined heart and liver transplantation is associated with an excellent outcome, with survival equivalent to HT alone. A recent review of experience at Mayo Clinic showed a 5-year survival of 75.8% (n = 18) for combined heart and liver transplantation for TTR amyloid, similar to HT alone.[52]

Furthermore, domino liver donation from combined heart-liver recipients is safe and has abrogated the burden on the limited donor organ pool. In effect, no additional donor livers are taken out of the pool. Older recipients with primarily cardiac manifestations may benefit from HT alone, but younger individuals should be considered for combined heart-liver transplantation to prevent systemic progression of the disease as well to effectively treat heart failure manifestations. Non-familial TTR amyloidosis, or SSA, most often affects older men but may occasionally surface at younger ages presenting with RCM/HCM phenotype. The heart is generally the only organ affected by amyloidosis, and systemic manifestations of amyloid are not typical. Isolated HT can therefore be considered as an appropriate therapy for patients otherwise meeting criteria for cardiac transplantation in which SSA has been diagnosed.

2.3 Hypertrophic cardiomyopathy and arrhythmogenic right ventricular dysplasia

In general, the indications for listing are similar to those for general cardiomyopathies; however, there are unique presentations of HCM requiring a specific recommendation. In general arrhythmogenic right ventricular dysplasia is a rare diagnosis, difficult to phenotypically characterize, and no specific recommendation can be made. Therefore, this entity is only minimally discussed.

Recommendation 2.3.1: Patients with severe heart failure and non-obstructive HCM not otherwise amenable to other treatment interventions should be considered for HT. Particular attention should be given to those patients with LV dilation and systolic dysfunction (Class I, Level of Evidence: B).

The most advanced form of heart failure in HCM is end-stage (or "burned out") HCM, which arises in a small distinct sub-set of patients with non-obstructive disease (prevalence 3%).[76] Progression of heart failure is associated with conversion to systolic dysfunction (LV ejection fraction $<$ 50%) with a shift from the small ventricle and hypertrophic state to substantial LV remodeling (including LV wall thinning, cavity enlargement, and systolic dysfunction), which can mimic dilated cardiomyopathy.[76,77] The clinical courses of these patients are variable and unpredictable, with some patients remaining well compensated (even asymptomatic) for many years after systolic dysfunction arises. Occasionally, patients with non-obstructive HCM and preserved systolic function can develop severe refractory heart failure due to diastolic dysfunction and become candidates for HT. Timing between diagnosis of HCM and end-stage HCM has been reported to be between 4 and 10 years. Younger age and family members affected were independent risk factors for death or need for transplantation.[78] Survival of patients with HCM after HT (75%–100% at 5 years, 61%–94% at 10 years) is similar to or possibly more favorable than that for patients with other CVDs.[78–80]

ARVD/C is a genetically determined myocardial disease characterized by fibrofatty replacement of myocytes, mainly involving but not limited to the right ventricle.[81] The typical clinical expression is characterized by malignant ventricular arrhythmias, which often represent the onset of disease as well as the cause of the fatal outcome.[82,83] As opposed to RCM, in which a large fraction of affected patients might develop indications for HT, only a small proportion of ARVD/C patients need to be considered for transplant during their follow-up, and most patients have a prolonged disease course from the diagnosis to the time of death or transplant indication. Similarly, LV non-compaction represents a pathologic entity, genetically linked and often poorly characterized and diagnosed after transplantation in the explanted heart.[84] We acknowledge these conditions but choose to provide no specific recommendations regarding transplant candidacy in these unique pathologic entities.

Section III (special considerations): Infectious diseases

Screening and management of certain chronic or latent infections, including human immunodeficiency viral (HIV) infection, Chagas disease, tuberculosis, hepatitis B and C viral (HBV and HCV) infections, are included in these guidelines to assist physicians in categorizing these infections before HT and where possible reduce the risks of reactivation after HT. A vaccination protocol has also been included to prevent infection before and after HT.

3.1 Human immunodeficiency virus

Recommendations: 3.1.1 Selected HIV-positive candidates may be considered for HT if they have no active or prior opportunistic infections (progressive multifocal leukoencephalopathy or chronic intestinal cryptosporidiosis $>$1 month), are clinically stable and compliant on combination antiretroviral therapy (cART) for $>$3 months, have undetectable HIV RNA, and have CD4 counts $>$200 cells/μl for $>$3 months (Class IIa, Level of Evidence: C).

3.1.2 Transplant centers performing heart transplantation in HIV-positive candidates should have structured protocols with multidisciplinary teams, adequate access to pharmacologic expertise, therapeutic drug monitoring for immunosuppressants, and laboratory access to antiviral drug resistance testing as needed (Class I, Level of Evidence: C).

3.1.3 Candidates with a history of primary central nervous system lymphoma and visceral Kaposi sarcoma should not be considered for HT (Class III, Level of Evidence: B).

3.1.4 HIV-positive candidates with other resolved neoplasms, including squamous cell carcinoma of the skin, anogenital carcinoma in situ, and other solid organ tumors considered cured may be considered after an appropriate disease-free period (Class IIb, Level of Evidence: C).

Since the introduction of combination ART (cART) resulting in the prolonged survival of HIV-infected patients, HIV infection is no longer considered an absolute contraindication to solid-organ transplantation.[85]

CVD is more recently recognized as an increasing cause of morbidity and mortality in the HIV population who are surviving longer.[86] In an analysis of more than 3,000 successfully treated HIV-positive subjects with undetectable HIV RNA, those with CD4+ T-cell counts in excess of 500 cells/mm^3 experienced mortality rates similar to those expected from the general population. Within this treated population, the number 1 cause of death was CVD, which accounted for 31% of overall mortality.[86]

The pathogenesis of CVD in HIV-positive patients is related to direct and indirect effects of HIV infection on vessel structures and has been shown to be independent of traditional risk factors.[87] Recent studies have shown that HIV infection strongly interferes with the biology of several cellular targets such as macrophages and endothelial cells. Moreover, cART induces a profound derangement of lipid metabolism and inflammatory cytokine networks that are directly involved in atherogenesis and progressive impairment of the cardiovascular system.[87] There is emerging outcome data supporting HT in selected situations, including use of MCS in HIV patients at highly specialized centers.[88,89] In general, most centers still tend to shun HIV patients, an aspect that may require change through better scientific communication.[90] However, the management of cART and immunosuppressive therapy is extremely challenging and requires a concerted structured approach.[91]

3.2 Chagas disease

Chagas disease is an uncommon cause of cardiomyopathy leading to need for HT in countries where the disease is endemic. Owing to migrant populations and globalization, this is now a worldwide problem. Thus, all centers should develop protocols for screening of candidates and surveillance after transplantation for reactivation of disease.

Recommendations: 3.2.1 Universal screening for *Trypanosoma cruzi* infection should be performed in all HT candidates born in Latin America (Central and South America or Mexico), those who have spent significant time in Latin America, those with a Latin American mother, or those who have received unscreened blood products (Class I, Level of Evidence: C).

3.2.2 Serologic testing for the presence of infection should be done using 2 serologic assays with different formats and *Trypanosoma cruzi* antigen preparations. Thus, an initial positive test should be followed up with a confirmatory test (Class I, Level of Evidence: C).

3.2.3 Detection of *Trypanosoma cruzi* infection should prompt treatment with benznidazole (first-line) or nifurtimox (second-line) (Class I, Level of Evidence: C).

HT is now accepted as the treatment of choice for heart failure caused by Chagas disease, despite the risks of reactivation of *Trypanosoma cruzi* infection. The annual reactivation incidence of this infection is high and varies from 18% to 22%.[92] For centers that offer HT to patients with Chagas cardiomyopathy, direct methods of parasite detection should be readily available.[92,93]

Treatment does not however confer immunity, and patients may reactivate while listed for transplantation and HT patients are prone to multiple reactivations during follow-up. The diagnosis of the acute-phase infection is achieved by direct parasitology tests, including a whole-blood preparation and a concentration method.[93,94] In the indeterminate and chronic stages, infection diagnosis is performed by serologic tests. All have good sensitivity but less than optimal specificity and show considerable variation in reproducibility and reliability of results. The most commonly used are the enzyme immunoassay, indirect hemagglutination, and indirect immunofluorescence method. Polymerase chain reaction (PCR)–based assays have been standardized and are now preferred. The World Health Organization recommends 2 tests for diagnosis of infection or disease. If active disease is confirmed, we recommend that such candidates be treated with the anti-parasite drug benznidazole (first-line) or nifurtimox (second-line). In certain countries, benznidazole is only available through a central regulatory process. As an example, in the United States, the Centers for Disease Control coordinates such use.

3.3 Tuberculosis

Recommendations: 3.3.1 All HT candidates should be screened for latent tuberculosis (TB) infection (LTBI) with a tuberculin skin test (TST) and/or interferon-γ release assay (IGRA) where available (Class I, Level of Evidence: B).

3.3.2 If a candidate has had a recent exposure to TB, or chest X-ray shows old TB (and inadequate or no treatment), 3 consecutive early morning sputum or bronchoalveolar lavage specimens should be obtained to exclude active TB disease (Class I, Level of Evidence: B).

3.3.3 Candidates with a positive IGRA or TST $\geq$ 5-mm induration should be treated pre-transplant with isoniazid, if tolerated. Candidates from a TB-endemic area with a positive IGRA or TST $\geq$ 5-mm induration should have at least 1 other risk factor (evidence of a recent seroconversion, evidence of old TB lung disease, history of untreated or inadequately treated TB, close contact with a person with TB) before commencing isoniazid prophylaxis. Add pyridoxine (25–50 mg/day) during isoniazid therapy to avoid peripheral neurotoxicity (Class I, Level of Evidence: B).

3.3.4 Treatment for LTBI should be for 6 to 9 months and should not interfere with the timing of transplantation. Patients should commence treatment as soon as possible before transplant and continue after transplant to compete a full course of therapy (Class I, Level of Evidence: B).

TB infection after HT is more commonly due to reactivation of LTBI in the recipient, although rarely it can be newly acquired or indeed transmitted from the donor.[95,96]

Screening for LTBI before transplantation is important given the high associated mortality and the significant challenges presented in diagnosis and managing this infection after transplantation.[97]

In addition to a detailed TB exposure history and chest imaging, the pre-transplant evaluation should include TST as well as an IGRA, where available, as the tests of choice. Because only 1% of patients with a positive pre-transplant TST result will eventually develop TB after transplant, such a finding should not delay transplantation, and therapy with isoniazid can be completed over a standard 6 to 9 months' time course. It is important to note that a 2-step TST is recommended, with a repeat TST 7 to 10 days after the first test (booster effect).[98]

In areas in which TB is endemic, a higher threshold for commencing isoniazid prophylaxis is the current practice, and patients are only considered for prophylaxis when a patient has a positive TST $\geq$ 5 mm and at least 1 other risk factor, such as recent seroconversion, evidence of old lung disease, history of untreated or inadequately treated TB, close contact with a person with TB, or receipt of an allograft from a donor with a history of untreated TB. A history of bacille Calmette-Guerin vaccination may render a positive TST and is therefore less specific. In such cases, the IGRA test is preferred.

3.4 HCV and HBV infections

Although acute or fulminant HBV and HCV infection is a contraindication, screening of HT candidates should be categorized into chronic or resolved infections, each with their specific considerations and risks.

Resolved HCV infection is defined by a clinical phenotype of HCV antibody positive, HCV RNA PCR negative, and normal synthetic liver function with a low risk of reactivation. Chronic HCV infection is defined by HCV RNA PCR positive or active use of HCV anti-viral drugs.

Prior HBV infection that is no longer active is characterized by HBV core antibody (HBc-Ab) positive and/or HBV surface antibody (HBs-Ab) positive but who remains HBV-surface antigen (HBsAg) negative (HBcAB-pos and/or HBsAB-pos but HBsAg-neg). Chronic HBV-infected candidates are defined as HBV surface antigen (HBsAg) positive or who are on HBV anti-viral drugs (Table 5).

Recommendations: 3.4.1 In candidates with resolved or prior inactive HCV infection, HCV RNA PCR testing should be performed at screening, at 3-month intervals while listed, and repeated at the time of transplantation (Class I, Level of Evidence: C).

3.4.2 In candidates with resolved or prior inactive HBV infection, serology and DNA viral load testing should be performed at screening, at 3-month intervals while listed, and repeated at time of transplantation. Complete viral HBV evaluation before transplantation should also include HBeAg and HBeAB, HBcAB, immunoglobulin G and M, and hepatitis delta virus (HDV) Ag, HDV AB, and serum α-fetoprotein (Class I, Level of Evidence: C).

3.4.3 In patients with chronic HCV infection, HCV genotype should be determined, and most patients will require a liver biopsy before active listing (Class I, Level of Evidence: C).

3.4.4 In patients with chronic HBV infection, liver biopsy should be done in all patients to exclude severe disease (Class I, Level of Evidence: C).

3.4.5 In patients with chronic HCV or HBV infection, clinical, radiologic or biochemical signs of cirrhosis, portal hypertension, or hepatocellular carcinoma are contraindications to HT (Class III, Level of Evidence: C).

Until recently, HCV infection was associated with decreased post-transplant outcome. However, newer anti-viral drugs have dramatically changed the landscape for this disease. The typical treatment of HCV infection consisted of pegylated interferon-α and ribavirin. This led to a sustained virologic response in 50% to 65% of patients with HCV genotype 1 or 4 and 75% to 80% with HCV genotype 2 or 3. However, these drugs have significant adverse effects and

Table 5 Definitions of Hepatitis B Virus Serology Profiles[a]

HBc-Ab	HBs-Ab	HBs-Ag	IgM HBc-Ab	Definition
−	−	−		No infection
−	+	−		Vaccinated
+	+	−		Resolved HBV infection
+	−	+	+	Acute infection
+	−	+	−	Chronic HBV infection
+	−	−		Interpretation unclear; 4 possibilities 1. Resolved infection (most common) 2. False-positive anti-HBc 3. "Low level" chronic infection 4. 4. Resolving acute infection

HBc-Ab, hepatitis B core antibody; HBs-Ab, hepatitis B surface antibody; HBs-Ag, hepatitis B surface antigen; IgM HBc-Ab, immunoglobulin M antibody to hepatitis B core antigen.

[a]Adapted from: Mast EE, Margolis HS, Fiore AE, et al; Advisory Committee on Immunization Practices (ACIP). A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part 1: immunization of infants, children, and adolescents. MMWR Recomm Rep 2005;54(RR-16):1-31.

are not tolerated by patients with advanced heart failure. The new direct-acting anti-viral drugs targeting viral proteins show promising results, with sustained virologic response in 80% to 90% of patients and without the intolerability encountered by previous regimens.[99,100] The high level of anti-viral efficacy, acceptable safety profile, and expected less interaction with immunosuppressive regimens of direct-acting anti-viral drugs will change our view on chronic HCV infection and transplantation in the coming years.

Owing to differential therapeutic responses, determination of HCV genotype is important.[101,102] In HCV genotype 2 and 3, anti-viral treatment should be started. If the HCV RNA clears, then a liver biopsy should be considered to establish absence of severe hepatic pathology. If the biopsy specimen shows mild to moderate disease, then the candidate can be listed for transplantation. If virus does not clear completely with anti-viral treatment, the patient may still be considered for HT transplantation as long as a liver biopsy specimen demonstrates no more than mild disease. This group has a less predictable course after transplantation and may be considered only at highly specialized centers with expertise in this area and availability of liver transplantation.

A liver biopsy should always be performed for non-genotype 2 or 3, and anti-viral treatment should be considered if the specimen shows mild disease. If the virus clears after anti-viral treatment, the candidate can be listed for HT. If the virus does not clear with anti-viral treatment and there are no other contraindications, the candidate can be considered for transplant only on a case-by-case basis because such patients remain at high risk for complications after transplantation. If the virus does not clear with anti-viral therapy and review of the biopsy specimen shows bridging fibrosis, the patient is not a candidate for isolated HT.

The risk of reactivation in those with resolved prior HBV infection is unknown in HT, but when extrapolated from liver and kidney transplant data, is considered low ($<2\%$).[103] Serology, including HBsAg, HBsAb, and HBcAb, should be performed in all candidates. If a candidate is HBsAg and HBsAb negative and only HBcAb positive, this might be a false-positive test or may represent a patient in a seroconversion window; therefore, HBV DNA testing should also be done in such individuals. Candidates with only HBsAb are most likely vaccinated and should be considered non-infected. Chronically infected HBV patients on treatment with a low viral load can be evaluated for HT but only in centers where there are joint established programs in hepatology and HT.

3.5 Vaccine-preventable infections in HT candidates

Recommendation: 3.5.1 Assessment of vaccination history and serologic protection is recommended during the transplant evaluation (Table 6) to afford ample opportunity to provide interventions before transplantation (Class I, Level of Evidence: C).

Vaccination is an important component of the pre-transplant assessment and care plan, representing an opportunity to diminish the effect of vaccine-preventable diseases in HT recipients.[104] Vaccination and/or revaccination are suggested before transplantation if candidates lack evidence of seroprotection on screening serology. Immunization guidelines vary from country to country and are frequently updated. Current national immunization guidelines should be consulted as vaccine recommendations for specific patients are developed. Generally, live viral vaccination is not recommended in the post-transplant period outside of controlled research studies; therefore, the emphasis for live viral vaccination (varicella, herpes zoster, mumps measles rubella [MMR], yellow fever) should be in the pre-transplant period. Measles outbreaks continue to be reported in the community, and disease may be acquired during a local outbreak or while travelling. Therefore, when possible, MMR serology should be checked before transplant and the transplant candidate immunized. Primary varicella can lead to severe complications after transplant. Like MMR, varicella vaccine is a live attenuated viral vaccine that is indicated before transplant in seronegative persons. Varicella zoster virus serology should be checked before transplant and the transplant candidate immunized if negative. Herpes zoster vaccine is another live-attenuated vaccine that has been shown in large randomized trials to prevent shingles and post-herpetic neuralgia. Consideration should be given to avoid administration of live viral vaccination within 3 to 4 weeks of anticipated transplantation. Close contacts, including family members and health care workers, should be fully immunized, including yearly influenza vaccination.[105]

Section IV (special considerations): CHD

A large proportion of candidates for HT now include children with CHD or adult survivors of CHD. Such patients have unique problems, including sensitization and reasons to require transplantation in the absence of overt heart failure (failing Fontan circulation), making it difficult to bridge these candidates to a successful transplantation in a timely manner. Thus, we present a series of recommendations to guide listing for these unique transplant candidates.

Recommendations: 4.1.1 HT for CHD should only be performed at centers with established medical and surgical experience in both adult CHD and transplantation (Class I, Level of Evidence: C).

4.1.2 All candidates with CHD should undergo detailed assessment of the position and anatomy of the abnormalities within the chest (via cardiac magnetic resonance imaging or chest computed tomography) to guide the surgical strategy, evaluation of PVR, and identification of all potential sources of pulmonary flow, assessment of patency of major veins and arteries and venous collaterals across the chest wall, presence of chronic or previous infections, presence of disease in organ systems that can affect post-transplant care and/or cannot be reversed with transplantation, qualitative

Table 6 Vaccination Protocol for Heart Transplant Candidates

Vaccine	Pre-transplant serology	Pre-transplant vaccination	Confirm response pre-transplant	Special circumstances
Hepatitis A	Yes[a]	Yes[a]	Yes[a]	Recommended for those with increased risk travel or residence in high-risk areas, occupational, or lifestyle exposure risk
Hepatitis B	Yes	Yes	Yes	
Pneumococcus (conjugate or polysaccharide)	Consider	Yes	Consider	Recommendation for conjugate vaccine, followed 8 weeks later by polysaccharide vaccine
Tetanus (dT)	Yes	Yes[a]	No	Administer Tdap to all who have not previously received Tdap
Pertussis (Tdap)	No	Yes[a]	No	Administer Tdap to all who have not previously received Tdap
Influenza	No	Yes	No	Seasonally, vaccination also recommended for close contacts
Meningococcus	No	Yes[a]	No	Recommended for those at increased risk including asplenia/polysplenia, high-risk travel, terminal complement deficit, including prior to eculizumab
Rabies	No	No[a]	No	Consider for those with risk of significant post-transplant exposure
Human papilloma virus	No	Yes[a]	No	Approved age 9–26 years
Live viral vaccines[b]				
Varicella	Yes	Yes[a]	Yes	Not needed if seropositive
Herpes zoster		Consider		
Mumps, measles, rubella	Yes	Yes[a]	Yes[a]	Not needed if born before 1957

dT, diphtheria and tetanus toxoids; Tdap, tetanus, diphtheria, pertussis.
[a]See special circumstances.
[b]Consideration should be given to avoid administration of live viral vaccination within 4 weeks of anticipated transplantation.

and quantitative assessment of anti-human leucocyte antigen (HLA) antibodies to specific HLA antigens, and evaluation of the psychosocial milieu of the patient and the patient's family that may affect post-transplant management. (Class I, Level of Evidence: C)

4.1.3 HT should be considered in certain anatomic and physiologic conditions with or without associated ventricular dysfunction. These conditions may include surgically uncorrectable severe stenosis(es) or atresia in the proximal coronary arteries, severe stenosis and/or insufficiency in systemic ventricular valves, severe arterial oxygen desaturation from a cardiac cause, persistent protein-losing enteropathy and/or plastic bronchitis associated with CHD despite optimal medical-surgical therapy, and pulmonary hypertension with the potential risk of developing fixed, irreversible elevation of PVR that could preclude HT in the future (Class IIa, Level of Evidence: C).

4.1.4. HT alone should not be performed in patients with severe, irreversible disease in other organ systems or when it is part of a severe, irreversible multisystemic disease process. In such cases, multiorgan transplantation may be considered (Class III, Level of Evidence: C).

4.1.5 HT alone should not be performed in the presence of severe hypoplasia of the central branch pulmonary arteries or pulmonary veins or as routine primary therapy for any specific congenital heart lesion before attempted or considered surgical repair (Class III, Level of Evidence: C).

Most transplants in CHD occur after previous reparative or palliative surgery.[106,107] Heart failure may evolve days to years after congenital heart surgery in both biventricular and single-ventricle lesions. Multifactorial causes of heart failure besides myocardial dysfunction include pulmonary hypertension and elevated PVR, persistent intracardiac shunts, ventricular outflow obstructions, valve disease, and electrophysiologic issues. Standard medical therapies for heart failure from adult trials appear to be less efficacious in heart failure in patients with single-ventricle lesions and/or systemic ventricles with a right ventricular morphology.[108] Recent analyses suggest that previous surgery for CHD is a risk marker for increased mortality after HT but that careful attention to selection and preparation have brought modern outcomes of CHD with HT at par with other indications.[109,110]

Evaluation considerations. With the exception of severe hypoplasia of the pulmonary arteries and veins, the myriad cardiac, arterial, and venous anatomies encountered after previous surgery for CHD do not generally prohibit HT. Previous sternotomies and surgeries lead to surgical adhesions that translate to increased ischemic times and bleeding, which can have an adverse effect on outcomes.[111]

Clear delineation of intrathoracic anatomy within the chest via cardiac magnetic resonance imaging or chest computed tomography aid in planning bypass cannulation and surgical strategies. In this regard, a detailed knowledge of prior operations is essential.

Aortopulmonary collaterals are increasingly recognized during the course of multiple single-ventricle palliations and can contribute to surgical bleeding and complicate the transplant procedure. New cardiac magnetic resonance techniques can quantify collateral flow and have shown that it may occur from macroscopic and microscopic collaterals.[112] Aortopulmonary collateral flow can prolong recovery after palliative procedures, and the volume overload from large aortopulmonary collaterals has been associated with primary graft failure after transplantation in this population.[113] Evaluation of flow and/or coil embolization of large collaterals before transplant may be useful in this population.

Previous congenital heart surgeries are frequently associated with thrombosis of central veins[114] that may limit access to the heart during the transplant procedure and for long-term surveillance procedures. A careful assessment of venous and arterial access before transplant can ensure that vessels are maintained for the ultimate performance of endomyocardial biopsies and cardiac catheterization. Careful evaluation of pulmonary hypertension and elevated resistance are especially important in these patients due their adverse effect on morbidity and mortality after transplantation. In children, the reversibility of PVR is more crucial than a specific baseline value[115] in determining the success of heart transplantation.

The exposure to blood products and human homograft material associated with surgery for CHD increases risk for the presence of anti-HLA antibodies (pre-sensitization). Children with elevated PRAs are at increased risk for adverse outcomes after transplantation,[116] but experience from multiple single centers[117,118] indicates some children can undergo a successful transplant across a positive crossmatch. Any evaluation of a child for HT after previous surgery for CHD should include an evaluation for the presence of anti-HLA antibodies beyond the simple PRA determination to allow for the elucidation of specific HLA antigens to which there are antibodies in the candidate to facilitate for a "virtual" crossmatch[119] before transplant.

The role of cardiopulmonary exercise testing to predict prognosis has been investigated in the adult CHD (ACHD) population. In a study of 335 consecutive ACHD patients, Diller et al[120] found peak V_{O_2} was lower in CHD patients than in healthy age-comparable controls. Furthermore, peak V_{O_2} predicted hospitalization and mortality, thereby identifying ACHD patients at increased risk. In the largest cardiopulmonary series to date, a cohort of 1,375 consecutive ACHD patients, peakV_{O_2}, heart rate reserve, and expired volume (V_E)/rate of carbon dioxide elimination (V_{CO_2}) slope (in noncyanotic patients) were related to 5-year survival.[121] The differential interpretation of peak V_{O_2} limitations has been confirmed in Fontan, Ebstein anomaly, and tetralogy of Fallot patients as well as other CHDs.[122]

Prognosis and outcomes. Davies et al[123] analyzed the United Network of Organ Sharing database and identified PVR index >6 Woods units/m^2, creatinine clearance <40 ml/min, hepatitis C seropositivity, age <1 year, and PRA $>40\%$ as high-risk factors at listing associated with an increased risk for mortality. Patients with ≥ 3 of these high-risk factors had a 12-month survival of $<60\%$ after transplant.[123] Other markers shown to estimate prognosis in acquired heart failure have been studied and found to have prognostic significance in CHD. These include anemia in non-cyanotic patients, hyponatremia, moderate to severe lung dysfunction (mean forced expiratory volume in 1 second of $52.1\% \pm 10.3\%$ predicted and forced vital capacity of $48.8\% \pm 8.8\%$ predicted), and renal dysfunction. Although biomarkers such as BNP have been shown to correlate with CHD outcomes, levels vary widely based on CHD diagnosis, and hence, the utility of BNP to discriminate prognosis is not as clear as that seen with acquired heart failure.[124] Various studies have identified imaging features associated with increased risk in CHD, including late gadolinium enhancement on magnetic resonance imaging.[125] Atrioventricular arrhythmias portend an increased risk of morbidity and mortality in CHD patients.[126]

Although numerous prognostic variables have been identified, the use of any individual marker may not accurately predict the need for or timing of transplantation. A major limitation of prognostic variables in CHD is that studies to date are hampered by inclusion of patients with multiple different CHD conditions, including those with and without cyanotic heart disease, or they are CHD-specific but with small numbers, with relatively short follow-up and low overall event rates. Unlike in acquired heart failure, prognostic models, such as the SHFM, have not been tested in CHD.

An increased Model for End-Stage Liver Disease (MELD) score has been associated with mortality in patients undergoing surgery in CHD syndromes with improved performance in the modern era.[110] MELD and modified MELD (mod-MELD) scores (substituting albumin for the international normalized ratio in patients on anti-coagulation) have been shown to be a predictor of mortality after HT (mod-MELD >20) and MCS.[127,128] Baseline MELD-XI (MELD excluding international normalized ratio) has been associated with an increased risk of a composite end point of sudden death, death from congestive heart failure, or cardiac transplantation in Fontan patients (hazard ratio of 7.76 [95% confidence interval, 2.05–29.33] for high MELD-XI score group vs low MELD-XI score; $p = 0.008$).[129]

The hepatic venous pressure gradient is the wedged hepatic venous pressure minus the free hepatic venous pressure gradient and a value ≥ 10 mm Hg has been associated with underlying portal hypertension and histologic cirrhosis.[130] Although this variable has not been studied prospectively in HT candidates, based on the literature to date, it may represent a reasonable threshold to predict increased risk.

The presence of "irreversible" end-organ dysfunction has been an established contraindication to pediatric HT. Identifying and defining irreversible end-organ dysfunction can be challenging. Analyses of combined heart-liver and heart-kidney transplants suggest combined transplants can be performed without prohibitive additional risk compared with HT alone, but a heart-kidney option may not be feasible in infants.[52,131]

Fontan circulation. Heart failure is a well-known complication that occurs with increasing frequency with long-term follow-up after palliation of single-ventricle lesions by the Fontan procedure.[132] A previous Fontan procedure increases mortality after HT[133] and is also associated with diseases in the gastrointestinal tract (protein-losing enteropathy) and lungs (plastic bronchitis) that can be life threatening. Protein-losing enteropathy and plastic bronchitis may occur in such patients even when ventricular function appears to be preserved and venous pressures do not appear to be extraordinarily elevated, a situation often referred to as a failure of the Fontan circulation or physiology as opposed to heart failure.[133,134] HT has been performed for protein-losing enteropathy and plastic bronchitis in pediatric Fontan patients and appears to lead to resolution of these complications in most recipients.[135,136] However some single-center studies have suggested that HT performed in Fontan patients with poor ventricular function may have better outcomes than those with normal ventricular function.[137]

As long-term experience with the Fontan procedure has accumulated, it has become evident that cirrhosis of the liver is a frequent long-term complication in these patients.[138] Cirrhosis can be frequently observed in hepatic imaging of pediatric Fontan HT candidates. Although some centers have opted for heart-liver transplantation in this setting,[139] the initial experience in another center[140] has indicated these findings may not always preclude short-term success with heart-only transplant. This experience suggests hepatic evaluation is an important component of the HT evaluation for Fontan patients. The nature and degree of hepatic disease that would determine the need for heart-only vs heart-liver transplantation needs to be established.

Other considerations. Transplant programs may consider minimizing risk by avoiding use of older donors or donors with long ischemic times. Specifically, the risk of death at 1 year increased from 15% to 40% for a 40-year-old ACHD recipient of a 50-year-old donor by extending donor ischemic time from <3 hours to >5 hours.[141] It is not the intention of this guideline to limit use of organs for transplantation but to encourage better recipient and organ matching in an effort to enhance outcome. CHD patients have complex medical and surgical issues and should be assessed at transplant centers with multidisciplinary expertise in transplantation and CHD. CHD patients should undergo transplantation at centers with high volumes[142] and expertise in CHD, anesthesia, and CHD surgery as well as heart failure, MCS, and transplantation. Collaborative approaches are ideal given not only the complexity of the cardiac condition but also associated conditions that may affect outcomes.

5.0 Use of Marijuana: Medical and legalized (inhalational and ingestible)

This is a highly controversial area, one in which there is little evidence to guide decision making, and of similar importance in those candidates being considered for listing as children or adults. In studies of the use of cannabis, a higher incidence of using other illicit drugs or mind-altering agents is noted.[143] Similarly, a higher risk of affective disorders and impaired cognition is encountered. In organ transplantation, concerns of heightened pre-disposition to fungal infections have been reported.[144,145] Whether candidates on medical marijuana or those that obtain it through other legal means should receive organ transplantation is at best an issue for which no clear direction exists, just as access to alcohol is legal, yet abuse renders a potential candidate unsuitable for transplantation. We similarly advise caution for centers in listing candidates unable to give up use of cannabis or those with such heavy use that cognitive ability is impaired, which could lead to medication non-adherence. At this time, each center will need to develop its own specific criteria for adjudicating candidacy for marijuana users.

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