

SPECIAL FEATURE

The international society of heart and lung transplantation guidelines for the care of heart transplant recipients

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J Heart Lung Transplant 2010;29:914–956

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Since the dawn of heart transplantation in the 1960s, the medical care of heart transplant recipients has been guided by the experience of individual clinicians and has varied from center to center. Despite many advances in surgical techniques, diagnostic approaches, and immunosuppressive strategies, survival after heart transplantation is limited by the development of cardiac allograft vasculopathy and by the adverse effects of immunosuppression. The International Society for Heart and Lung Transplantation (ISHLT) has made an unprecedented commitment to convene experts in all areas of heart transplantation to develop practice guidelines for the care of heart transplant recipients. After a vast effort involving 40 writers from 9 countries worldwide, the *ISHLT Guidelines for the Care of Heart Transplant Recipients* have now been completed and the Executive Summary of these guidelines is the subject of this article.

The document results from the work of 3 Task Force groups:

- Task Force 1 addresses the peri-operative care of heart transplant recipients, including the surgical issues affecting early post-operative care; monitoring and treatment of early hemodynamic, metabolic, and infectious issues; evaluation and treatment of allosensitization; evaluation and treatment of early coagulopathies; the organization of a multidisciplinary care team; management of ABO “incompatible” pediatric heart transplantation; and the use of extracorporeal membrane oxygenation (ECMO) for the hemodynamic support of pediatric recipients.
- Task Force 2 discusses the mechanisms, diagnosis, and treatment of heart transplant rejection; the mechanisms of action, dosing, and drug level monitoring of immunosuppressive drugs as well as their adverse effects and interactions with concomitantly used medications; and reviews the major clinical trials and the immunosuppressive strategies to be used in special clinical situations.
- Task Force 3 covers the myriad of clinical issues occurring long-term after heart transplantation, including cardiac allograft vasculopathy, the chronic adverse effects of immunosuppression (neurotoxicity, renal insufficiency, hypertension, bone disease, diabetes and malignancy), as well as reproductive health,

exercise, psychologic problems, return to work, and operation of motor vehicles after heart transplantation.

It is important to note that each task force was co-chaired by a pediatric heart transplant physician who had the specific mandate to highlight issues unique to the pediatric heart transplant population and to ensure their adequate representation.

As the reader will undoubtedly observe, most of the recommendations only achieve a Level of Evidence C, indicating that these recommendations are based on expert consensus and not on randomized controlled clinical trials. A concerted effort was also made to highlight the numerous gaps in evidence pertaining to many aspects of the care of heart transplant recipients. This lack of “evidence-based” recommendations is mostly due to the limited number of heart transplant recipients worldwide. However, it is the hope of all contributing writers and reviewers that the increased awareness of the “gaps in evidence” provided by these guidelines will spur further research in many important areas of heart transplantation.

Task Force 1: Peri-operative Care of the Heart Transplant Recipient

Chair: Maria Rosa Costanzo, MD; *Co-Chairs:* Anne Dipchand, MD; Randall Starling, MD

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Topic 1: Surgical Issues Impacting Care in the Immediate Post-operative Period

Recommendations on Donor Heart Selection:^{1,2} *Class IIa:*

1. Taking into consideration only the variable of “donor age,” the hearts of donors younger than 45 years will invariably have sufficient reserves to withstand the rigors of heart transplant (HT) even in settings of prolonged ischemic time, recipient comorbidities, and multiple previous recipient operations with hemodynamically destabilizing bleed-

ing. Hearts from donors between the ages of 45 and 55 years should probably be used when the projected ischemic time is ≤ 4 hours and the potential recipient does not have comorbidities or surgical issues where anything less than robust donor heart performance could prove fatal. The use of donor hearts > 55 years should only be used if the survival benefit of HT for a recipient unequivocally exceeds the decrement in early HT survival due to transplantation of a heart with limited myocardial reserves.

Level of Evidence: B.

Recommendation on the Transplantation of Hearts from Donors with Infection³:

Class IIa:

1. Hearts from donors with severe infection can be used provided that (1) the donor infection is community acquired and donor death occurs rapidly (within 96 hours); (2) repeat blood cultures before organ procurement are negative; (3) pathogen-specific anti-microbial therapy is administered to the donor; (4) donor myocardial function is normal; and (5) there is no evidence of endocarditis by direct inspection of the donor heart. If such hearts are used for transplantation, the recipient should undergo surveillance blood cultures on the first post-operative day and pathogen-specific anti-biotic therapy should be administered for an appropriate duration of time.

Level of Evidence: C.

Recommendation on the Transplantation of Hearts from Donors with Potential Drug Toxicities:⁴⁻⁸

Class IIa:

1. Hearts from donors with a history of past or current non-intravenous (IV) cocaine abuse can be used for transplantation provided cardiac function is normal and LVH is absent.

Level of Evidence: C.

2. In light of current information, the use of hearts from donors with a history of "alcohol abuse" remains uncertain, but it should probably be considered unwise.

Level of Evidence: C.

3. The use of hearts from donors who have died of carbon monoxide intoxication can be recommended with caution, although the safety has not been completely established. It is recommended that these hearts be used provided there is a normal donor electrocardiogram (ECG) and echocardiogram, minimal elevation of cardiac markers, minimal inotropic requirements, a relatively short ischemic time, a favorable donor to recipient weight ratio and a recipient with normal pulmonary vascular resistance.

Level of Evidence: C.

Recommendations on the Use of Donors with Pre-existing Cardiac Abnormalities:^{9,10}

Class I:

1. As far as the function is concerned, a donor heart should not be used in the presence of intractable ventricular arrhythmias, the need for excessive inotropic support (dopamine at a dose of 20 $\mu\text{g}/\text{kg}/\text{min}$ or similar doses of

other adrenergic agents despite aggressive optimization of pre-load and after-load), discreet wall motion abnormalities on echocardiography or left ventricular ejection fraction (LVEF) $< 40\%$ despite optimization of hemodynamics with inotropic support.

Level of Evidence: B.

2. A donor heart with a normally functioning bicuspid aortic valve can be used for HT. Anatomically and hemodynamically abnormal aortic and mitral valves may undergo bench repair or replacement with subsequent transplantation of the heart.

Level of Evidence: C.

Class IIa:

1. The use of donor hearts with obstructive disease in any major coronary artery should be avoided unless the heart is being considered for the alternate list recipients with concomitant coronary bypass surgery.

Level of Evidence: C.

2. It would seem appropriate to use hearts from donors with left ventricular hypertrophy (LVH) provided it is not associated with ECG findings of LVH and LV wall thickness is < 14 mm.

Level of Evidence: C.

Recommendations on Donor Cardiac Function:

Class I:

1. As far as the function is concerned, a donor heart should not be used in the presence of intractable ventricular arrhythmias, the need for excessive inotropic support (dopamine at a dose of 20 $\text{mcg}/\text{kg}/\text{min}$ or similar doses of other adrenergic agents despite aggressive optimization of preload and after load), discreet wall motion abnormalities on echocardiography or LV ejection fraction $< 40\%$ despite optimization of hemodynamics with inotropic support.

Level of Evidence: B.

Recommendations on Donor-Recipient Size Matching:^{11,12}

Class I:

1. As a general rule, the use of hearts from donors whose body weight is no greater than 30% below that of the recipient is uniformly safe. Furthermore, a male donor of average weight (70 kg) can be safely used for any size recipient irrespective of weight. Use of a female donor whose weight is more than 20% lower than that of a male recipient should be viewed with caution.

Level of Evidence: C.

Recommendations on Ischemic Times¹⁰:

Class I:

1. As a general rule the ischemic time should be less than 4 hours. However, there are situations in which ischemic times longer than 4 hours are anticipated. Donor hearts with ischemic times longer than 4 hours should only be accepted when other factors interacting with ischemic

Table 1 Properties of Intravenous Vasoactive Drugs Used after Heart Transplantation

	Peripheral vasoconstriction	Cardiac contractility	Peripheral vasodilation	Chronotropic effect	Arrhythmia risk
Isoproterenol	0	++++	+++	++++	++++
Dobutamine	0	+++	++	+	+
Dopamine	++	+++	+	+	+
Epinephrine	+++	++++	+	++	+++
Milrinone/enoximone	0	+++	+	++	++
Norepinephrine	++++	+++	0	+	+
Phenylephrine	++++	0	0	0	0
Vasopressin	++++	0	0	0	0

Adapted and reprinted with permission from Kirklin JK, et al.⁴⁶

time are ideal, including donor young age, normal cardiac function, and absence of inotropic support.

Level of Evidence: C.

Topic 2: Early Post-operative Care of the Heart Transplant Recipient

Recommendations on the Post-operative Monitoring of Heart Transplant Recipients:^{13–31}

Class I:

1. Peri-operative monitoring of heart transplant recipients should include (1) continuous ECG monitoring; (2) post-operative 12-lead ECG; (3) invasive arterial pressure monitoring; (4) direct measurement of right atrial pressure (RAP) or central venous pressure (CVP); (5) measurement of left atrial or pulmonary artery wedge pressure (PAWP); (6) intermittent measurement of cardiac output (CO); (7) continuous measurement of arterial oxygen saturation; (8) intraoperative transesophageal echocardiogram (TEE); (9) continuous assessment of urinary output.

Level of Evidence: C.

Recommendations on the Management of Peri-operative Tricuspid Valve Regurgitation:^{32,33}

Class I:

1. Tricuspid valve regurgitation identified intraoperatively and estimated to be moderate or severe (> 2+), should be re-evaluated by transthoracic echocardiogram (TTE) or TEE within 24 hours of HT and closely monitored for the first few post-operative days. The frequency of subsequent follow-up should be guided by clinical and hemodynamic variables.

Level of Evidence: C.

Class II:

1. DeVega annuloplasty of the donor tricuspid valve (TV) can be considered to maintain the normal size of the TV annulus.

Level of Evidence: C.

Recommendations on the Management of Peri-operative Pericardial Effusions:^{34,35}

Class I:

1. Pericardial effusions occurring after HT should be monitored by echocardiogram.
2. Percutaneous or surgical drainage should be done when the pericardial effusion causes hemodynamic compromise.

Level of Evidence: C.

Class IIa:

1. Pericardial effusions that are not hemodynamically compromising do not require drainage unless there is a strong suspicion of an infectious etiology.

Level of Evidence: C.

Recommendations for Peri-operative Vasoactive Drugs Use in Heart Transplant Recipients:^{36–46}

(See Table 1)

Class I:

1. Continuous infusion of an inotropic agent should be used to maintain hemodynamic stability post-operatively. Inotropic agents should be weaned as tolerated over the first 3 to 5 days. The lowest effective dose should be used.

Level of Evidence: C.

2. The following therapies are suggested:
 - a. isoproterenol, 1 to 10 $\mu\text{g}/\text{min}$, *or*
 - b. dobutamine, 1 to 10 $\mu\text{g}/\text{kg}/\text{min}$ \pm dopamine 1 to 10 $\mu\text{g}/\text{kg}/\text{min}$, *or*
 - c. isoproterenol, 1 to 10 $\mu\text{g}/\text{min}$ \pm dopamine 1 to 10 $\mu\text{g}/\text{kg}/\text{min}$, *or*
 - d. milrinone, 0.375 to 0.75 $\mu\text{g}/\text{kg}/\text{min}$

Level of Evidence: C.

3. Continuous infusion of α -adrenergic agonists including phenylephrine, norepinephrine, or epinephrine can be used to maintain adequate mean arterial pressure.

Level of Evidence: C.

4. Low dose vasopressin (0.03–0.1 U/min) or methylene blue can be added to α -agonist for vasodilatory shock.

Level of Evidence: B.

Recommendations for the Medical Management of Right Ventricular Dysfunction and Pulmonary Vascular Hypertension After Heart Transplantation^{36–45,47}:

(See Figure 1)

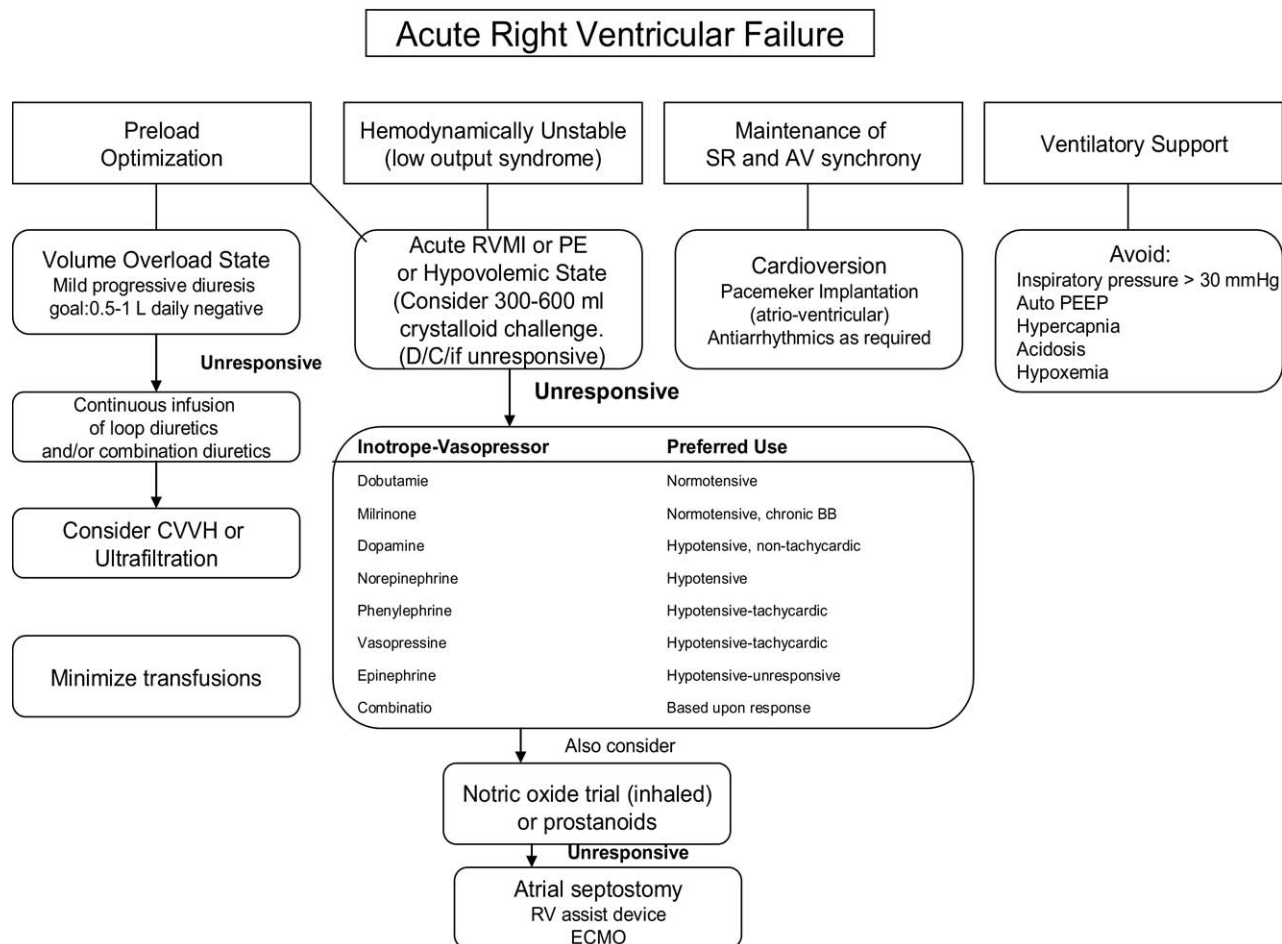


Figure 1 Management of right ventricular dysfunction. AV, atrioventricular; CVVH, continuous venovenous hemofiltration; MI, myocardial infarction; PE, pulmonary embolism; PEEP, positive end-expiratory pressure; SR, sinus rhythm. Adapted and reprinted with permission from Haddad F, et al.⁴⁷

Class I:

1. Inotropic agents that can be used to augment right ventricle (RV) function include isoproterenol, milrinone, enoximone, dobutamine, and epinephrine.

Level of Evidence: C.

Class IIa:

1. Systemic vasodilators with pulmonary vasodilating properties, including nitroglycerine and sodium nitroprusside, can be used in the absence of systemic hypotension.

Level of Evidence: C.

2. Selective pulmonary vasodilators that can be used in the management of peri-operative RV dysfunction include (1) prostaglandins (prostaglandin E1 [alprostadil], prostaglandin I2 [epoprostenol or prostacyclin], inhaled iloprost); (2) inhaled nitric oxide; (3) sildenafil.

Level of Evidence: C.

Recommendations on the Peri-operative Use of Mechanical Circulatory Support After Heart Transplantation:⁴⁸⁻⁵²

Class I:

1. Mechanical circulatory support (MCS) should be initiated early if there is failure to wean from cardiopulmo-

nary bypass (CPB) or other evidence of heart allograft failure such as the requirement for multiple high-dose inotropic agents to permit separation from CPB.

Level of Evidence: B.

2. MCS should be considered if there is continued or worsening hemodynamic instability, such as decreasing cardiac index (CI) and a falling MVO_2 or $MVO_2 < 50\%$ that is not corrected by appropriate resuscitation.

Level of Evidence: B.

3. Support for either LV or RV failure should escalate from pharmacotherapy to IABP to MCS.

Level of Evidence: B.

4. Small ventricular assist devices (VADs) such as the TandemHeart and Levitronix Centrimag can provide adequate support for RV, LV, or biventricular (BiV) failure, and have benefits of ease of implantation, management, and explant.

Level of Evidence: C.

Class IIa:

1. In the presence of hemodynamic instability, cardiac tamponade should be excluded by direct surgical exploration. The presence of hyperacute/antibody-mediated rejection should also be excluded. If hemodynamic

instability persists in the absence of cardiac tamponade, MCS should be considered.

Level of Evidence: C.

2. The timing MCS discontinuation should be guided by evidence of graft recovery. If there is no evidence of graft functional recovery within 3 to 4 days, hyperacute and antibody-mediated rejection should be excluded and the option of listing for repeat HT may be considered.

Level of Evidence: C.

Class IIb:

1. Use of ECMO support in adults requires consideration of the risk of infection, immobility, and need for anticoagulation.

Level of Evidence: C.

Recommendations for the Management of Early Heart Allograft Dysfunction in Pediatric Recipients:^{53–60}

Class IIb:

1. The increased risk of post-operative RV dysfunction must be carefully evaluated in children, although evidence suggests that children can safely undergo HT despite elevation of pulmonary vascular resistance (PVR) above values considered unsafe in adults.

Level of Evidence: C.

2. Contrary to the experience and practice in adults, the first choice for support in the setting of primary graft failure (PGF) in the pediatric setting should be ECMO.

Class IIa, Level of Evidence C.

Recommendations for the Peri-operative Management of Cardiac Arrhythmias in Heart Transplant Recipients:^{61–67}

Class I:

1. Pharmacologic chronotropic agents, including isoproterenol and theophylline can be used in the peri-operative setting to increase heart rate.

Level of Evidence: B.

2. Atrial and ventricular temporary epicardial pacing wires should be placed at the time of HT even if the initial rhythm is sinus.

Level of Evidence: B.

3. After HT, temporary pacing should be initiated in the setting of relative bradycardia to maintain heart rates of > 90 beats/min.

Level of Evidence: B.

4. Pacing guidelines of the American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS) and the European Society of Cardiology (ESC) lack recommendations specific for temporary pacing early after HT. Recommendations for permanent pacing exist for inappropriate chronotropic response 3 weeks after HT. Standard atrium-paced, atrium-sensed, inhibited-rate modulation (AAIR) or dual-paced, dual-sensed, dual-response to sensing, rate modulation (DDDR) pacemakers are preferable.

Level of Evidence: C.

5. Treatment of tachyarrhythmias should be aimed at rate control.

Level of Evidence: B.

6. Persistent tachyarrhythmias, whether atrial or ventricular, should prompt investigation of possible rejection and electrophysiological evaluation if rejection is absent.

Level of Evidence: B.

7. Sustained ventricular tachycardia (SVT) should be evaluated with both an angiogram and an endomyocardial biopsy (EMB).

Level of Evidence: B.

Class IIa:

1. The Class III anti-arrhythmics sotalol and amiodarone can be safely used in HT recipients and have minimal interaction with immunosuppressive agents.

Level of Evidence: C.

2. Non-dihydropyridine calcium channel blockers (CCBs) and β -blockers may be used in HT recipients for rate control.

Level of Evidence: B.

Recommendations for Peri-operative Renal Function and Fluid Status Management in Heart Transplant Recipients:^{68–71}

Class I:

1. The CVP should be maintained between 5 and 12 mm Hg, a level that provides adequate cardiac filling pressures without causing RV overload.

Level of Evidence: C.

2. Colloid replacement is generally preferred in the first 24 hours after HT; blood, if indicated, is the first choice.

Level Evidence: C.

3. Compatible blood products may be safely administered after HT without increasing the risk for rejection. In the setting of ABO incompatible pediatric HT special care must be taken in the selection of compatible products to account for both donor and recipient blood types.

Level of Evidence: B.

4. Blood products should be leukocyte-depleted. Blood products should be cytomegalovirus (CMV) negative if donor and recipient are CMV negative.

Level of Evidence: B.

5. IV loop diuretics are used to decrease volume overload. In addition to intermittent IV bolus, continuous IV infusion of loop diuretics with or without sequential nephron blockade using thiazide diuretics or aldosterone antagonists may be necessary.

Level of Evidence: C.

6. Hemodialysis for renal failure should be initiated early for both volume management and renal replacement. If the recipient is anuric, oliguric, or has a sharp rise in sCr within 2 to 4 hours after HT, then hemodialysis may be necessary.

Level of Evidence: B.

Class IIa:

1. Ultrafiltration should be considered if RAP remains elevated (> 20 mm Hg) despite pharmacologic interventions.

Level of Evidence: B.

Class IIb:

1. Delay of initiation of calcineurin inhibitor (CNI) therapy should be considered if there is significant pre-operative renal insufficiency or deterioration of kidney function in the first 2 post-operative days.

Level of Evidence: C.

Recommendations for the Peri-operative Management of Hyperglycemia in Heart Transplant Recipient:^{72,73}

Class I:

1. Oral hypoglycemic agents should be discontinued pre-operatively.

Level Evidence: C.

Class IIa:

1. A continuous infusion insulin regimen should be used to maintain blood glucose below 200 mg/dL during the intensive care unit (ICU) stay.

Level of Evidence: B.

2. Aggressive management of hyperglycemia should be continued for the duration of hospitalization.

Level of Evidence: C.

Recommendations for Anti-bacterial Prophylaxis/Treatment⁷⁴:

Class I:

1. Pre-operative anti-biotic prophylaxis should be used before the transplant operation.

Level of Evidence: B.

2. Drugs should be selected based upon their activity against usual skin flora, specifically *Staphylococcus* species.

Level of Evidence: B.

3. If a chronically infected device such as a VAD or a pacemaker is present, then peri-operative anti-biotics should be selected based on microbiologic sensitivities.

Level of Evidence: B.

4. In the event that the donor had an ongoing bacterial infection, a course of suitable anti-biotics should be considered.

Level of Evidence: B.

Recommendations for Peri-operative Anti-viral Prophylaxis in Heart Transplant Recipients⁷⁵:

(See Table 2)

Class I:

1. Prophylaxis against CMV should be initiated within 24 to 48 hours after HT.

Level of Evidence: A.

2. The CMV serologic status of the donor and recipient may be used to stratify the patient as low-risk, intermediate-risk, or high-risk for developing a CMV infection.

Table 2 Typical Recommendations for the Prevention of Cytomegalovirus in Heart Transplant Recipients

Group	Recommendations/Options
D+/R-	Oral ganciclovir (1000 g PO TID) or valganciclovir (900 mg PO/day) for 3 months
	<i>or</i>
	IV ganciclovir (5–10 mg/kg/day) for 1–3 months Preemptive therapy generally not preferred due to high risk of disease Some HT centers will add CMV immune globulin for high risk patients
R+	Oral ganciclovir (1000 g PO TID) or valganciclovir (900 mg PO/day) for 3 months
	<i>or</i>
	IV ganciclovir (5–10 mg/kg/day) for 1–3 months
	<i>or</i> Preemptive therapy. Monitor with nucleic acid testing or CMV antigenemia assay Therapy with IV ganciclovir or oral valganciclovir

CMV, cytomegalovirus; D, donor; HT, heart transplant; IV, intravenous; PO, oral (per os); R, recipient; TID, 3 times daily.

Level of Evidence: A.

3. Intravenous ganciclovir may be administered to intermediate and high-risk patients, whereas patients at low-risk for CMV infection may only receive anti-herpes simplex virus prophylaxis with acyclovir. (See Table 3.)

Level of Evidence: A.

Recommendations for Peri-operative Anti-Fungal Prophylaxis in Heart Transplant Recipients⁷⁶:

Class I:

1. Anti-fungal prophylaxis to prevent mucocutaneous candidiasis should be initiated once the recipient is extubated. The agents most commonly used are nystatin (4–6 mL [400,000 to 600,000 units] 4 times daily, swish and swallow) or clotrimazole lozenges (10 mg).

Level of Evidence: C.

Recommendations for Anti-Protozoal Prophylaxis in Heart Transplant Recipients⁷⁷:

Class I:

1. Prophylaxis against *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) pneumonia and *Toxoplasma gondii* (in indicated cases) should also be initiated in the early post-operative period. Trimethoprim/sulfamethoxazole (80 mg TMP/160 mg SMZ, 1 single- or double-strength tablet per day) is the most commonly used medication. In the setting of a sulfa allergy or glucose-6-phosphate dehydrogenase deficiency, alternative regimens can be used, including: (1) Aerosolized pentamidine (AP) isethionate (300 mg every 3–4 weeks). (2) Dapsone (diaminodiphenylsulfone) with or without TMP or pyrimethamine (50–100 mg/day). Pyrimethamine may be administered weekly (25 or 50 mg) to supplement dapsone (50–100 mg/day). Dapsone is metabolized

Table 3 Examples of Desensitization Therapies

Therapy	Dose	Frequency
Plasmapheresis	(A, F) 1.5 volume exchanges	(A) 5 consecutive days (B) 5 times, every other day (C) 2–3 times/week until transplant (D) 5 times, every other day, every 2–4 weeks
Intravenous immunoglobulin (IV Ig)	(A, B) 2g/kg IV divided over 2 days (C) 2–3 g/kg IV divided over 4 days (D) 0.1 mg/kg IV (E) 100 mg/kg IV (F) 20 g (of 10% IV Ig)	(A) Every 2–4 weeks (D) Every 2–4 weeks (E) Every 4 weeks
Rituximab	(G) 150 g (of 10% IV Ig) divided over 3 rounds (A) 1 g IV (C, E) 375 mg/m ² (G) 500 mg	(G) Every 4 weeks (A) Weekly × 4 (C) ×2 doses (E) Weekly × 4 (G) Every 2 weeks
Cyclophosphamide (used in the past)	(A) 1 mg/kg orally (C) 0.5 μg/m ² (D) 1 mg/kg orally	(A) Daily

(A) UCLA; (B) Stanford University; (C) University of Maryland; (D) University of Toronto; (E) University of Wisconsin; (F) Loyola University Chicago; (G) University of Berlin.

Adapted from Kobashigawa J, et al.⁸⁰

via the hepatic cytochrome P-450 system (CYP3A). (3) Atovaquone (1500 mg PO QD). (4) Clindamycin and pyrimethamine.

Level of Evidence: B.

Recommendations for Peri-operative Infection Prophylaxis and Treatment in Pediatric Heart Transplant Recipients:^{74–77}

Class IIb:

1. IV anti-fungal prophylaxis should be considered for infants (< 1 year of age) with an open chest and/or requiring ECMO support in the peri-operative period.

Level of Evidence: C.

2. Prophylaxis for *Pneumocystis jiroveci* should be instituted for a minimum of 3 months up to a maximum of 24 months after HT.

Level of Evidence: C.

Topic 3: Evaluation of Allosensitization, Approaches to Sensitized Heart Transplant Recipients, and Hyperacute and Delayed Antibody-Mediated Rejection

Recommendations for the Evaluation of Donor/Recipient Histocompatibility:^{78–84}

Class I:

1. Screening panel reactive antibodies (PRA) should be performed in all HT candidates. When the PRA is elevated ($\geq 10\%$) further evaluation is recommended.

Level of Evidence: C.

2. The specificity of circulating antibodies should be determined with a solid-phase assay such as flow-cytometry,

if possible, in a regional certified human leukocyte antigen (HLA) laboratory.

Level of Evidence: C.

3. The complement fixation capability of detected antibodies should be reported.

Level of Evidence: C.

4. The anti-HLA class I and II specificities (ie, any HLA antibody directed against HLA-A, HLA-B, HLA-Cw, HLA-DR, and HLA-DQ antigens) should be defined. In the absence of international standards, each transplant center must define the threshold of antibody levels used to define which specific donor HLA antigens confer an unacceptable rejection risk.

Level of Evidence: C.

5. The virtual crossmatch, which compares recipient anti-HLA antibody specificities with donor HLA antigens, should be routinely used to increase the donor pool for sensitized recipients.

Level of Evidence: C.

Recommendations for the Risk-Assessment and Prophylaxis Strategies for Allosensitized Heart Transplant Candidates^{80,85}:

(See Table 3)

Class IIa:

1. A complete patient sensitization history, including previous PRA determinations, blood transfusions, pregnancies, implant of homograft materials, previous transplantation, and use of a VAD is required to assess the risk of heart allograft anti-body-mediated rejection.

Level of Evidence: C.

Table 4 Panel-Reactive Antibody Screening Frequency After Original Assessment

PRA	Number of heart transplant centers screening at each interval								Total
	1 mon	2 mon	3 mon	4–6 mon	1 year	Variable	SE	Other	
Negative	10	2	8	16	7	4	16	2	65
Positive	33	8	6	2	65

PRA, panel reactive antibody; SE, sensitizing events.

Adapted from Betkowski AS, et al.⁷⁸

- A PRA $\geq 10\%$ indicates significant allosensitization and it should raise the question of whether therapies aimed at reducing allosensitization should be instituted to minimize the need for a prospective donor/recipient crossmatch.

Level of Evidence: C.

- The results of the retrospective donor recipient crossmatch may be considered to make decisions regarding immunosuppressive therapy.

Level of Evidence: C.

Class IIb:

- Desensitization therapy should be considered when the calculated PRA is considered by the individual transplant center to be high enough to significantly decrease the likelihood for a compatible donor match or to decrease the likelihood of donor heart rejection where unavoidable mismatches occur.

Level of Evidence: C.

- Choices to consider as desensitization therapies include IV immunoglobulin (Ig) infusion, plasmapheresis, either alone or combined, rituximab, and in very selected cases, splenectomy.

Level of Evidence: C.

- A large randomized controlled clinical trial is needed to assess the effectiveness of desensitization strategies and their impact on outcomes after HT.

Level of Evidence: C.

Recommendations for Monitoring of Allosensitization Status of Heart Transplant Candidates and Recipients^{78,80,85}: (Table 4)

Class IIb:

- The presence of anti-HLA antibodies should be regularly monitored in allosensitized patients undergoing desensitizing therapies until a compatible heart allograft becomes available.

Level of Evidence: C.

- In ambulatory, non-sensitized HT candidates it is reasonable to measure anti-HLA antibodies every 6 months.

Level of Evidence: C.

- In HT candidates requiring blood transfusions, anti-HLA antibodies determination should be repeated 2 to 4 weeks later and prospective donor/recipient crossmatch is required in the interim period if a suitable donor organ becomes available.

Level of Evidence: C.

- No uniform recommendations exist as to the frequency of anti-HLA antibody determinations after an infection or during MCS.

Level of Evidence: C.

- Circulating immunoglobulins should be measured before and after plasmapheresis or immunoabsorption.

Level of Evidence: C.

- Lymphocyte sub-populations should be measured before and after the use of rituximab.

Level of Evidence: C.

- In addition to the post-operative retrospective crossmatch, donor-specific antibodies levels should be obtained when antibody-mediated rejection (AMR) is suspected or confirmed by EMB.

Level of Evidence: C.

Recommendations for the Treatment of Antibody-Mediated Rejection:^{80,86}

Class IIa:

- Initial therapy of AMR can include immunoabsorption and corticosteroid (CS) or plasmapheresis/low dose of IV Ig and CS.

Level of Evidence: C.

- Rituximab can be added to reduce the risk of recurrent rejection.

Level of Evidence: C.

- Changes in therapy, which can be considered for maintenance immunosuppression in patients who experience AMR, can include switch to tacrolimus (TAC) in patients receiving cyclosporine (CYA)-based immunosuppression, increased doses of mycophenolate mofetil (MMF), and CS.

Level of Evidence: C.

Recommendations for the Approach to Allosensitization in Pediatric Heart Transplant Recipients:^{76,77,87}

Class IIb:

- The HT can be carried out in highly sensitized pediatric patients without a prospective crossmatch or virtual crossmatch at centers experienced in pediatric HT across a positive crossmatch.

Level of Evidence: C.

Topic 4: Management of ABO "Incompatible" Heart Transplant Recipients

Table 5 Match of Blood Products to Specific ABO-Incompatible Heart Transplant Scenario

Blood group		Red blood cells (plasma depleted)	Fresh frozen plasma	Cryoprecipitate	Platelets (managed similarly to plasma)	
Recipient's	Donor's					2nd choice
O	A	O	A	A	A	O concentrate
O	B	O	B	B	B	O concentrate
O	AB	O	AB	AB, A or B	AB	A or B concentrate
A	B	A	AB	AB, or B ^a	AB	B concentrate
A	AB	A	AB	AB, A or B ^a	AB	A or B concentrate
B	A	B	AB	AB, or A ^a	AB	A concentrate
B	AB	B	AB	AB, A or B ^a	AB	A or B concentrate

^aSecond choice.

Recommendations for the Selection of Candidates for ABO “Incompatible” Heart Transplant:^{88,89}

Class IIa:

1. The upper limit of age or isohemagglutinin titer for ABO-incompatible pediatric HT remains unclear.
Level of Evidence: C.
2. ABO-incompatible HT can be safely performed in the pediatric population in the presence of positive isohemagglutinin titers against the donor organ.
Level of Evidence: C.
3. ABO-incompatible HT, especially in the presence of donor-specific isohemagglutinins > 1:4, should be performed in an experienced center.
Level of Evidence: C.

Recommendation for the Intraoperative Care of ABO “Incompatible” Heart Transplant Recipients:^{88,89}

Class IIa:

1. ABO-incompatible HT can be undertaken by performing plasma exchange using the CPB circuit to remove donor specific isohemagglutinins.
Level of Evidence: C.
2. Plasma exchange using the CPB circuit allows the safe transplantation of ABO-incompatible organs without the need of aggressive pre-operative immunosuppressive therapies or splenectomy.
Level of Evidence: C.

Recommendations for the Monitoring of Isohemagglutinin Levels in ABO “Incompatible” Heart Transplant Recipients:^{88,90}

Class IIa:

1. Serial measurements of isohemagglutinin titers should be done in the post-operative period. Decisions about whether immunosuppressive therapy must be modified should be based not only on the change in isohemagglutinin titers but also on clinical or pathologic evidence of rejection.
Level of Evidence: C.

Recommendations for the Administration of Blood Products in ABO “Incompatible” Heart Transplant Recipients⁸⁸⁻⁹⁰:

(See Table 5)

Class IIa:

1. Whole blood products should never be administered to a child who has received an ABO-incompatible HT, and the families should be educated to communicate this fact to other caregivers in the case of any future medical emergency or surgery. Group O red blood cells and group AB blood elements are safe for every blood group combination.
Level of Evidence: C.
2. If red blood cells transfusions are given to any ABO-incompatible HT recipient, red blood cell units should be matched based on the HT recipient’s ABO blood type.
Level of Evidence: C.
3. If platelets and/or plasma preparations are needed in ABO-incompatible HT recipients, these blood products should be matched based on the donor’s ABO blood type.
Level of Evidence: C.

Recommendations for Immunosuppression in ABO “Incompatible” Heart Transplant Recipients:^{88,89,91}

Class IIa:

1. Standard (triple) immunosuppression with a CNI, an anti-proliferative agent, and CS can be used in children undergoing ABO-incompatible HT without an increased risk of rejection.
Level of Evidence: B.
2. Immunosuppression management beyond the peri-operative period is similar to that of the ABO-compatible pediatric HT population.
Level of Evidence: B.

*Recommendation for Rejection Surveillance in ABO “Incompatible” Heart Transplant Recipients:*⁸⁸⁻⁹⁰

Class IIa:

1. Rejection surveillance in ABO-incompatible HT recipients is the same as that of the ABO-compatible HT population.

Level of Evidence: C.

Topic 5: Coagulopathies in Heart Transplant Surgery

Recommendations for the Evaluation of Hemostasis in Heart Transplant Recipients⁹²:

Class I:

1. A history of bleeding (including details of family history, previous excessive post-traumatic or post-surgical bleeding) and of the use of any medications that alter coagulation should be obtained from the patient.

Level of Evidence: C.

2. Screening coagulation tests of prothrombin time (PT), activated partial thromboplastin time (aPTT), and platelets counts should be measured immediately before HT surgery.

Level of Evidence: C.

3. The activated clotting time (ACT) should be obtained at multiple points during the HT surgery to gauge the activity of heparin during each phase of the HT surgery.

Level of Evidence: C.

Class IIa:

1. Thromboelastography may be useful during the HT surgery to further elucidate the status of the patient's hemostasis.

Level of Evidence: C.

2. Platelet function can be measured either by platelet aggregometry or by a point of care assay such as the platelets function assay 100 (PFA-100) during the HT surgery.

Level of Evidence: C.

3. Fibrinogen levels and D-Dimer values should be measured post-operatively because these are tests of fibrinolysis and correlate with the risk of bleeding after HT surgery.

Level of Evidence: C.

4. Thromboelastography may be repeated after HT surgery to monitor patients' hemostasis.

Level of Evidence: C.

Recommendations for the Reversal of Anti-coagulation before Heart Transplantation:⁹³⁻⁹⁶

Class I:

1. Pre-operatively, the international normalized ratio (INR) should be reduced to ≤ 1.5 .

Level of Evidence: C.

2. Low doses of vitamin K (2.5–5.0 mg) given IV are preferable to high doses because they are associated with a lower risk of anaphylaxis.

Level of Evidence: C.

3. Given the need for rapid normalization of the INR, chronically anti-coagulated patients about to undergo HT should receive vitamin K in conjunction with fresh frozen plasma (FFP), prothrombin plasma concentrates (PCCs), or recombinant factor VII (rFVII), depending on their availability and the patient's renal and hepatic functions.

Level of Evidence: C.

Recommendations for Anti-coagulation in Heart Transplant Recipients:⁹⁷⁻⁹⁹

Class IIa:

1. The absence of platelet factor 4/heparin antibodies should be confirmed.

Level of Evidence: C.

2. The use of unfractionated heparin should be restricted to the operative procedure itself. Low-molecular-weight heparin is not recommended, due to a longer half-life than unfractionated heparin and the inability to fully reverse its effect with protamine.

Level of Evidence: C.

3. Alternative anti-coagulants can be used pre-operatively and post-operatively in patients with history of heparin-induced thrombocytopenia (HIT) in whom the platelet count has recovered but immunoglobulin G (IgG) antibodies to the platelet factor 4/heparin complex are still present.

Level of Evidence: C.

4. Patients with abnormal hepatic and normal renal function can be treated with lepirudin, danaparoid, or fondaparinux, whereas those with abnormal renal and normal hepatic function can receive argatroban at standard doses or lepirudin at reduced doses.

Level of Evidence: C.

5. Patients with both renal and hepatic dysfunction can be treated with argatroban or bivalirudin at reduced doses.

Level of Evidence: C.

Gaps in Evidence:

Transfusion strategies are not well studied. Consensus opinion drives the decision of when to transfuse blood products. Expert opinions on which clinical situations require transfusions are highly variable. Recombinant factor VIIa has not been tested in controlled clinical trials and therefore there is little evidence to support its use in a bleeding cardiac surgery patient. Tranexamic acid and aminocaproic acid have not been evaluated in a definitive randomized study. Very few studies have been performed specifically in HT recipients. Thus, the recommendations for HT are extrapolated from evidence regarding achievement of hemostasis in general cardiac surgery.

Recommendations for the Pharmacologic Management of Coagulopathies in Heart Transplant Recipients:¹⁰⁰⁻¹⁰⁵

Class I:

1. Transfusion of coagulation factors is necessary for adequate hemostasis. Thus, fresh frozen plasma and platelets should be transfused based on measured levels. Fibrinogen infusion for massive bleeding and inadequate fibrinogen levels is needed to control blood loss.

Level of Evidence: C.

Class IIa:

1. Tranexamic acid and epsilon-aminocaproic acid both have anti-fibrinolytic activity and can be used before CPB to reduce the risk of bleeding in selected patients.

Level of Evidence: B.

Class IIb:

1. Recombinant factor VIIa may be used in cases of intrac-table or excessive bleeding with HT surgery.

Level of Evidence: C.

Class III:

1. Although aprotinin can reduce bleeding during HT sur-gery, its routine use is not recommended due to an increased risk of adverse clinical events.

Level of Evidence: B.

2. Desmopressin is not recommended for routine use be-cause its modest reduction in bleeding has been associ-ated with adverse clinical events.

Level of Evidence: A.

Topic 6: Documentation and Communication with the Multidisciplinary Team

Recommendations for the Documentation and Communica-tion with the Multidisciplinary Team:^{106–108}

Class I:

1. Transplant centers must have a multidisciplinary ap-proach to patient management.

Level of Evidence: C.

2. The HT team should have regularly scheduled meetings of all disciplines involved.

Level of Evidence: C.

Class IIa:

1. Social work and psychiatry specialists should be inte-grated into the patient management team.

Level of Evidence: B.

2. Transplant centers should strive to have specialty-trained pharmacists or physicians with expertise in pharmacol-ogy as part of the multidisciplinary team.

Level of Evidence: B.

Class IIb:

1. Integration of input from pharmacists and infectious dis-ease specialists is important during the development of treatment protocols for HT recipients.

Level of Evidence: B.

2. Dieticians should be involved in the care of HT recipi-ents to provide input regarding prevention of weight gain and maintenance of glucose control.

Level of Evidence: C.

Topic 7: Use of Extracorporeal Membrane Oxygenation for the Management of Primary Graft Failure in Pediatric Heart Transplant Recipients

Recommendations on the Indications for Extracorporeal Membrane Oxygenation in Pediatric Heart Transplant Re-cipients^{109–114}:

(See Table 6)

Class IIa:

Table 6 Potential Causes of Primary Graft Failure After Pediatric Heart Transplantation

Donor issues

- Poor donor organ preservation
- Poor donor quality
 - Diminished echocardiographic ejection fraction
 - Requirement for high inotropic support
 - Elevated blood troponin I level
- Prolonged ischemic time
- Large donor (donor-to-recipient weight ratio > 2.0)
- Small donor (donor-to-recipient weight ratio < 1.0)
- Prolonged donor cardiopulmonary resuscitation times
- Anoxia as cause of death
- Non-identical blood type
- Donor age

Recipient issues

- Pre-transplantation diagnosis of congenital heart disease
- Previous sternotomy
- Elevated pulmonary vascular resistance
- Pre-transplantation need for extracorporeal membrane oxygenator
- Pre-transplantation need for ventilatory support

Adapted from Huddleston CB, et al.¹¹⁴

1. The use of ECMO should be considered when there is failure to separate from CPB after all correctable causes of such failure have been excluded.

Level of Evidence: C.

2. ECMO should be promptly instituted when progressive heart allograft dysfunction occurs post-operatively.

Level of Evidence: C.

Recommendations for the Conduct of ECMO Support in Pe-diatric Heart Transplant Recipients:^{115,116}

Class IIa:

1. The amount of circulatory support provided by ECMO should be sufficient to achieve adequate systemic perfu-sion and oxygen delivery while waiting for the myocar-dium to recover.

Level of Evidence: C.

2. Left heart distension during ECMO support should be aggressively treated because it will compromise pulmo-nary function and impede LV recovery.

Level of Evidence: C.

Recommendations for the Timing of Discontinuation of ECMO Support in the Setting of Primary Graft Failure¹¹⁷:

Class IIa:

1. Clinical and echocardiographic variables should be seri-ally assessed to determine if myocardial recovery is occurring.

Level of Evidence: C.

2. Objective signs of recovery should lead to weaning and discontinuation of ECMO support.

Level of Evidence: C.

Class IIb:

1. Lack of objective evidence of myocardial recovery within 3 to 5 days should prompt consideration of either institution of long term MCS as a bridge to recovery or HT or withdrawal of life-sustaining therapy.

Level of Evidence: C.

Gaps in Evidence:

1. The optimal modality for surveillance of adverse neurologic events during ECMO support for PGF is unknown.
2. Optimal infection prophylaxis in the immunosuppressed patient receiving ECMO support for PGF is unknown.
3. Optimal renal-sparing immunosuppression protocol(s) in patients receiving ECMO support for PGF is unknown.
4. The duration of time waiting for recovery of myocardial function in the setting of PGF beyond which recovery is unlikely is unknown.
5. The role of more intermediate and long-term MCS in patients with myocardial recovery insufficient to allow separation from ECMO within 5 to 7 days is unknown.
6. Risk factors for poor outcomes after retransplantation in ECMO-supported HT recipients are unknown.

Task Force 2: Immunosuppression and Rejection

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Topic 1: Rejection Surveillance

Recommendations for Rejection Surveillance by Endomyocardial Biopsy in Heart Transplant Recipients:¹¹⁸⁻¹²⁰

Class IIa:

1. It is reasonable to utilize EMB in a HT candidate suspected of having an infiltrative cardiomyopathy or an inflammatory process, such as giant cell myocarditis, amyloidosis, or sarcoidosis.

Level of Evidence: C.

2. The standard of care for adult HT recipients is to perform periodic EMB during the first 6 to 12 post-operative months for surveillance of HT rejection.

Level of Evidence: C.

3. The standard of care in adolescents should be similar to that in adults, including surveillance EMB for heart allograft rejection for 6 to 12 months after HT. In younger children, especially infants, it is reasonable to utilize echocardiography as a screening tool to reduce the frequency of EMB.

Level of Evidence: C.

4. After the first post-operative year, EMB surveillance for an extended period of time (eg, every 4–6 months) is recommended in HT recipients at higher risk for late acute rejection, to reduce the risk for rejection with

hemodynamic compromise, and to reduce the risk of death in African-American recipients.

Level of Evidence: C.

Class IIb:

4. The use of routine EMB later than 5 years after HT is optional in both adults and children, depending on clinical judgment and the risk for late allograft rejection.

Level of Evidence: C.

Recommendations for the Non-Invasive Monitoring of Acute Heart Transplant Rejection:¹²⁰⁻¹³⁵

Class IIa:

1. In centers with proven expertise in ventricular evoked potentials (VER) monitoring, intramyocardial electrograms recorded non-invasively with telemetric pacemakers can be used for rejection surveillance in patients at low risk for rejection.

Level of Evidence: C.

2. Gene Expression Profiling (Allomap) can be used to rule out the presence of ACR of grade 2R or greater in appropriate low-risk patients, between 6 months and 5 years after HT.

Level of Evidence: B.

Class IIb:

1. Use of echocardiography as primary monitoring modality for acute heart allograft rejection in infants can be considered as an alternative to surveillance EMB.

Level of Evidence: C.

Class III:

1. The routine clinical use of electrocardiographic parameters for acute heart allograft rejection monitoring is not recommended.

Level of Evidence: C.

2. The use of echocardiography as an alternative to EMB for rejection monitoring is not recommended.

Level of Evidence: C.

3. The routine clinical use of MRI for acute allograft rejection monitoring is not recommended.

Level of Evidence: C.

4. The use of brain natriuretic peptide (BNP), troponin I or T, or C-reactive protein (CRP) levels for acute heart allograft rejection monitoring is not recommended.

Level of Evidence: C.

5. The use of systemic inflammatory markers for acute heart allograft rejection monitoring is not recommended.

Level of Evidence: C.

6. Routine use of non-invasive testing modalities (ECG, imaging, or biomarkers) is not recommended as the primary method for acute heart allograft rejection surveillance in older children and adolescents.

Level of Evidence: C.

Topic 2: Monitoring of Immunosuppressive Drug Levels

Table 7 Drugs That Affect the Levels of Tacrolimus, Cyclosporine, Sirolimus, and Everolimus

Decrease immunosuppression levels	Increase immunosuppression levels
Anti-epileptics	Anti-microbials
Carbamazepine	Clarithromycin
Fosphenytoin	Erythromycin
Phenobarbital	Metronidazole and tinidazole
Phenytoin	Quinupristin/dalfopristin
	Levofloxacin
Anti-microbials	Anti-fungals
Caspofungin	Clotrimazole
Nafacillin	Itraconazole
Rifabutin	Ketoconazole
Rifampin	Fluconazole
Rifapentine	Posaconazole
	Voriconazole
Anti-retroviral Therapy	Anti-retroviral therapy
Efavirenz	Protease inhibitors (general)
Etravirine	Amprenavir
Nevirapine	Atazanavir
	Darunavir
	Fosamprenavir
	Indinavir
	Nelfinavir
	Ritonavir
	Saquinavir
	Tipranavir
Others	Cardiovascular
Antacids containing magnesium, calcium, or aluminum (tacrolimus only)	Amiodarone
Deferasirox	Diltiazem
Modafinil	Verapamil
St. John's wort	
Thalidomide	
Ticlopidine	
Troglitazone	
	Nutraceuticals
	Bitter orange
	Grapefruit juice
	Others
	Rilonacept
	Theophylline
	Cimetidine
	Fluvoxamine
	Glipizide
	Glyburide
	Imatinib
	Nefazodone

Recommendations for the Monitoring of Immunosuppressive Drug Levels^{136–149}:

(See Table 7)

Class I:

1. The use of the microemulsion formulation of CYA is recommended because it is associated with more favorable pharmacokinetic features compared with the oil-based compound.

Level of Evidence: B.**Class IIa:**

1. At present, 2-hour post-dose (C2) levels should not replace 12-hour trough (C0) concentrations for routine monitoring of CYA exposure in most patients, but may be useful in selected patients in whom a better characterization of the pharmacokinetic profile of CYA is desired.

Level of Evidence: B.

2. Measurement of 12-hour trough CYA concentration is the recommended form of therapeutic drug monitoring for routine clinical use. The target levels are dependent on the method used (high-performance liquid chromatography [HPLC] vs enzyme multiplied immunoassay technique [EMIT] vs cloned enzyme donor immunoassay method [CEDIA]), concomitant immunosuppression, toxicity risks, and time after HT. In general, when used in conjunction with azathioprine (AZA) or a mycophenolic acid (MPA) preparation, the average CYA trough concentration target using the Abbot TDX assay (or equivalent) is 325 ng/ml (range, 275–375 ng/ml) for the first 6 post-operative weeks, 275 ng/ml (range 200–350 ng/ml) for Weeks 6 to 12, 225 ng/ml (range 150–300 ng/ml) for Month 3 to Month 6, and 200 ng/ml (range 150–250 ng/ml) from Month 6 onwards.

Level of Evidence: C.

3. At present, CYA trough concentration targets when CYA is used in combination with proliferation signal inhibitor (PSI; mammalian target of rapamycin [mTOR] inhibitors) agents have not been adequately determined.

Level of Evidence: C.

4. Measurement of 12-hour trough concentration for twice-daily TAC and a 24-hour trough concentration for once-daily TAC is the recommended drug monitoring method for routine clinical use. The therapeutic range of TAC levels varies depending on concomitant drugs, toxicity concerns, and time after HT. In general, when used in conjunction with AZA or a MPA preparation, TAC trough concentration targets range between 10 and 15 ng/ml during the early post-operative period (Days 0–60), between 8 and 12 ng/ml for the next 3 to 6 months, and between 5 and 10 ng/ml in stable patients 6 months after HT.

Level of Evidence: C.

5. At this time, target therapeutic TAC trough concentrations when TAC is used in combination with PSI (mTOR inhibitors) agents have not been adequately determined.

Level of Evidence: C.

6. Therapeutic drug monitoring for PSIs using trough concentration levels is recommended for sirolimus (SRL) and everolimus (EVL). Levels should be measured at least 5 days after adjustment of the dose, when a new steady state is achieved. When used in combination with CYA, the optimal trough target level for EVL is between 3 and 8 ng/ml. The corresponding optimal trough level for SRL is 4 to 12 ng/ml.

Level of Evidence: B.

Table 8 Significant Differences in Primary End Points between Study Groups from Major Clinical Trials

Author (year)	Study	N	Follow-up	Survival	Rejection	CAV by IVUS
Kobashigawa ¹⁶³ (1998)	MMF vs AZA	650	3 years	MMF = higher survival ^a	MMF = less rejection	NS; MMF = less CAV at 1 year ^b
Reichart ²⁰⁹ (1998)	TAC vs CYA	82	1 year	NS	NS	
Taylor ¹⁵³ (1999)	TAC vs CYA	85	1 year	NS	NS	
Eisen ¹⁵⁷ (2003)	EVL vs AZA	634	1 year	NS	EVL groups = less rejection	EVL groups = less CAV
Keogh ¹⁵⁶ (2004)	SRL vs AZA	136	2 years	NS	SRL groups = less rejection at 6 months	SRL groups = less CAV
Grimm ¹⁵⁴ (2006)	TAC vs CYA	314	1.5 year	NS	TAC = less rejection at 6 months	...
Kobashigawa ¹⁵⁸ (2006)	TAC/MMF vs TAC/SRL vs CYA/MMF	343	1 year	NS	NS; TAC groups = lower any-treated rejection	...
Baran ¹⁵⁹ (2007)	TAC/MMF vs TAC	58	1 year	NS	NS	NS
Lehmkuhl ¹⁶⁰ (2008)	EVL/rd-CYA vs MMFsd-CYA	176	1 year	NS	NS	...

CAV, cardiac allograft vasculopathy; CYA, cyclosporine; EVL, everolimus; EVL/rd, everolimus/reduced exposure; IVUS, intravascular ultrasound; MMF, mycophenolate mofetil; MMFsd, mycophenolate mofetil/standard exposure; NS, not statistically significant; SRL, sirolimus; TAC, tacrolimus.

^aTreated-patient population (see text).

^bReanalysis of MMF IVUS data.²⁰⁹

7. In pediatric HT recipients, TAC and CYA should be monitored using C0 levels when twice-daily dosing is used. Target levels are comparable to those in adults, but slightly lower targets may be used in low-risk patients such as non-sensitized infant HT recipients.

Level of Evidence: C.

8. There are insufficient data to support routine monitoring of MPA levels in pediatric recipients. However, intermittent monitoring is reasonable when there is ongoing rejection, doubts about adequacy of dosing (eg, infants and young children), and to assess medical compliance.

Level of Evidence: C.

Class IIb:

1. At this time replacement of twice-daily TAC with once-daily TAC dosing cannot be recommended in HT recipients. Should a patient require the once-daily formulation, appropriate monitoring should be used to ensure maintenance of appropriate levels and preserved heart allograft function.

Level of Evidence: C.

2. In patients with a therapeutic 12-hour trough concentration for twice daily TAC but evidence of potential drug-related toxicity or reduced efficacy (rejection), a 3-hour post-dose level (C3) may help to adjust TAC doses.

Level of Evidence: C.

3. In selected situations (rejection, infection, renal failure, malnutrition, and certain ethnic populations) where it is suspected that altered MMF exposure contributes to heart allograft dysfunction, measurement of trough MPA levels may be used to guide drug dosing. In such cases, a MPA level of < 1.5 mg/liter is considered to be sub-therapeutic.

Level of Evidence: C.

4. Dose adjustments and frequency of therapy with polyclonal antibodies (eg, anti-thymocyte globulin) used as induction therapy can be monitored with daily measurement of CD3 or CD2 counts with the goal of maintaining the CD2 or CD3 count between 25 and 50 cells/mm³ or absolute total lymphocyte counts < 100 to 200 cells/mm³.

Level of Evidence: C.

5. In pediatric HT recipients CYA C2 monitoring may be performed instead of C0 in centers with extensive experience with this form of monitoring.

Level of Evidence: C.

6. As in adults, routine monitoring of SRL and EVL at C0 is recommended also in children.

Level of Evidence: C.

Class III:

1. Routine therapeutic drug monitoring of MPA levels to adjust MMF doses cannot be recommended at this time.

Level of Evidence: C.

2. Measuring CD 25 saturation to adjust the dose of anti-interleukin-2 receptor antibodies remains experimental and its routine clinical use cannot be recommended.

Level of Evidence: C.

Topic 3: Principles of Immunosuppression and Recommended Regimens

Recommendations on the Principles of Immunosuppressive Regimens in Heart Transplant Recipients¹⁵⁰⁻²¹⁰:

(See Table 8, Table 9A, Table 9B, and Table 10)

Class I:

1. Maintenance therapy should include a CNI in all pediatric HT recipients.

Table 9 (A) Significant Differences in Adverse Events From the Major Clinical Trials

First author (year)	Study	No.	Renal function	Infections	Cholesterol & triglycerides	Hypertension
Kobashigawa ¹⁶³ (1998)	MMF vs AZA	650		MMF = more any opportunistic infection		
Reichart ²⁰⁹ (1998)	TAC vs CYA	82	NS	NS		CYA = more hypertension
Taylor ¹⁵³ (1999)	TAC vs CYA	85	NS	NS	CYA = higher chol & tri	CYA = more hypertension
Eisen ¹⁵⁷ (2003)	EVL vs AZA	634	EVL groups = worse renal function	EVL groups = lower viral/CMV but more bacterial infections	EVL groups = higher chol & tri	NS
Keogh ¹⁵⁶ (2004)	SRL vs AZA	136	SRL groups = worse renal function	SRL groups = lower CMV but more pneumonia	NS for chol; SRL groups = higher trig	NS
Grimm ¹⁵⁴ (2006)	TAC vs CYA	314	NS	NS	CYA = higher chol & tri	CYA = more hypertension
Kobashigawa ¹⁵⁸ (2006)	TAC/MMF vs TAC/SRL vs CYA/MMF	343	TAC/MMF = best renal function	TAC/SRL = lower viral but more fungal infections	NS for chol; TAC/MMF = lower trig	NS
Baran ¹⁵⁹ (2007)	TAC/MMF vs TAC	58	NS	TAC/MMF = more hospitalized infections
Lehmkuhl ¹⁶⁰ (2008)	EVL/rd-CYA vs MMFsd-CYA	176	NS	EVL = Less CMV infections

See Table 8 for abbreviations.

Level of Evidence: C.

- In adults, the use of statins beginning 1 to 2 weeks after HT is recommended regardless of cholesterol levels. Owing to pharmacologic interactions with CNI and risk for toxicity, initial statin doses should be lower than those recommended for hyperlipidemia.

Level of Evidence: A.

- Creatinine kinase levels should be monitored in all children receiving statins.

Level of Evidence: C.

Class IIa:

- Calcineurin inhibitor-based therapy remains the standard in immunosuppressive protocols used after HT.

Level of Evidence: B.

- MMF, EVL, or SRL as tolerated, should be included in contemporary immunosuppressive regimens because therapies including these drugs have been shown to reduce onset and progression of cardiac allograft vasculopathy (CAV) as assessed by intravascular ultrasound (IVUS).

Level of Evidence: B.

- Immunosuppressive induction with polyclonal antibody preparations may be beneficial in patients at high risk of renal dysfunction when used with the intent to delay or avoid the use of a CNI.

Level of Evidence: B.

- In pediatric HT recipients, routine use of induction therapy with a polyclonal preparation is indicated when complete CS avoidance is planned after HT.

Level of Evidence: C.

- Routine use of statins is recommended for all pediatric patients with evidence of hyperlipidemia, CAV, or after retransplantation.

Level of Evidence: C.

- TAC is the preferred CNI for pediatric HT recipients considered at high immunologic risk (eg, sensitized recipients with evidence of donor-specific antibody [DSA]).

Level of Evidence: C.

- CS avoidance, early CS weaning, or very low dose maintenance CS therapy are all acceptable therapeutic approaches.

Level of Evidence: B.

Table 9 (B) Significant Differences in Adverse Events From the Major Clinical Trials

First author (year)	Study	N	Hematologic	GI Disorders	Other
Kobashigawa ¹⁶³ (1998)	MMF vs AZA	650	AZA = more leukopenia	MMF = more diarrhea and esophagitis	NS for hyperglycemia treatment
Reichart ²⁰⁹ (1998)	TAC vs CYA	82	NS for glucose intolerance
Taylor ¹⁵³ (1999)	TAC vs CYA	85	NS
Eisen ¹⁵⁷ (2003)	EVL vs AZA	634	NS	NS	NS for wound infection
Keogh ¹⁵⁶ (2004)	SRL vs AZA	136	SRL groups = more anemia & thrombocytopenia	AZA = more nausea; SRL groups = more diarrhea	AZA = more arrhythmia and atrial fibrillation; SRL groups = more mouth ulcers & abnormal healing
Grimm ¹⁵⁴ (2006)	TAC vs CYA	314	TAC = more anemia	CYA = more cholelithiasis	TAC = more diabetes mellitus & tremor; CYA = more gum hyperplasia & hirsutism
Kobashigawa ¹⁵⁸ (2006)	TAC/MMF vs TAC/SRL vs CYA/MMF	343	NS	...	TAC/SRL = more insulin therapy & impaired wound healing; NS for diabetes mellitus
Baran ¹⁵⁹ (2007)	TAC/MMF vs TAC	58	NS	...	NS for malignancy
Lehmkuhl ¹⁶⁰ (2008)	EVL/rd-CYA vs MMFsd-CYA	176	MMF = more leukopenia

See Table 8 for abbreviations.

8. If used, CS weaning should be attempted if there are significant CS side effects and no recent rejection episodes (eg, within 6 months).

Level of Evidence: C.

9. Pediatric recipients with pre-formed alloantibodies and a positive donor-specific cross-match should receive induction therapy, and TAC-based "triple therapy" with CSs and either MMF or an mTOR inhibitor.

Level of Evidence: C.

Class IIb:

1. The results of clinical trials suggest that TAC-based regimens may be associated with lower rejection rates but not with superior survival after HT than CYA-based regimens.

Level of Evidence: B.

Table 10 Recommendation for Statin Doses in Heart Transplant Patients^{201,202,210,387-393}

Drug	Dose	Risks
Pravastatin	20-40 mg ³⁹⁴	Myositis (lower)
Simvastatin	5-20 mg ³⁹⁵	Myositis (higher)
	> 20 mg not recommended	
Atorvastatin	10-20 mg ³⁸⁷	Myositis (higher)
Fluvastatin	40-80 mg ³⁸⁹	Myositis (lower)
Lovastatin	20 mg ³⁹⁰	Myositis (higher)
Rosuvastatin	5-20 mg ³⁸⁸	Myositis

2. The adverse events of immunosuppressive drugs observed in randomized clinical trials underscore the need for individualization of immunosuppression according to the characteristics and risks of the individual HT recipient.

Level of Evidence: C.

3. Most children should receive adjunctive therapy with an anti-metabolite or a PSI.

Level of Evidence: C.

4. If a child is intolerant of adjunctive therapy, the decision whether or not to replace it with another agent should be made after review of the patient's rejection history and immunologic risk. TAC monotherapy is acceptable in patients with a benign rejection history.

Level of Evidence: C.

5. For children diagnosed with CAV, the addition of an mTOR inhibitor should be strongly considered.

Level of Evidence: C.

6. Routine use of immunosuppressive induction in all patients has not been shown to be superior to immunosuppressive regimens that do not use such therapy.

Level of Evidence: B.

7. Immunosuppressive induction with anti-thymocyte globulin (ATG) may be beneficial in patients at high risk for acute rejection.

Level of Evidence: C.

8. Routine use of statins is recommended for adolescents and selected younger children with an increased risk of rejection or CAV.

Level of Evidence: C.

Table 11 Suggested Dosing of Medications Used for Treatment of Acute Cellular Rejection

Medication	Dose	Duration
Corticosteroids		
Methylprednisolone (high-dose)	250–1000 mg/day IV	3 days ^a
Prednisone	1–3 mg/kg/day PO	3–5 days ^a
Polyclonal anti-thymocyte antibody		
Thymoglobulin ^b	0.75–1.5 mg/kg/day	5–14 days
ATGAM ^b	10 mg/kg/day	5–14 days
ATG-Fresenius ^b	3 mg/kg/day	5–14 days
Monoclonal antibody		
Muromonab-CD3 (OKT3) ^b	5 mg/day	5–14 days

ATG, anti-thymocyte gamma-globulin-fresenius; ATGAM, anti-thymocyte gamma-globulin; IV, intravenous; PO, oral (per os).

^aCorticosteroid taper can be considered.

^bPremedicate with CS, anti-histamine and anti-pyretic.

Topic 4: Treatment of Acute Cellular Rejection

Recommendations for Treatment of Symptomatic Acute Cellular Rejection^{205–207,211–217}:

(See Table 11)

Class I:

1. An EMB should be performed as early as possible if there is suspicion of symptomatic acute heart allograft rejection.

Level of Evidence: C.

2. The HT recipient with symptomatic acute cellular rejection should be hospitalized. Patients with hemodynamic compromise should be treated in the ICU.

Level of Evidence: C.

3. High-dose IV CS should be first-line therapy for symptomatic acute cellular rejection irrespective of ISHLT EMB grade (1R, 2R or 3R).

Level of Evidence: C.

4. Cytolytic immunosuppressive therapy with anti-thymocyte antibodies should be administered in addition to IV CS if hemodynamic compromise is present, and especially if there is no clinical improvement within 12 to 24 hours of IV CS administration.

Level of Evidence: C.

5. IV inotropes and vasopressors should be used as necessary to maintain adequate CO and systemic blood pressure until recovery of heart allograft function occurs.

Level of Evidence: C.

6. Anti-microbial prophylaxis against opportunistic infections should be administered when high-dose CS and/or cytolytic therapy are used for the treatment of rejection.

Level of Evidence: C.

7. Appropriate adjustments of maintenance immunosuppressive therapy should be made to decrease the risk of recurrent rejection. These can include ascertain-

ment of compliance with current therapy, increase in the dose of current immunosuppressive agent(s), addition of new agent(s), or conversion to different agent(s).

Level of Evidence: C.

8. Follow-up EMB should be done 1 to 2 weeks after initiation of therapy for acute cellular rejection.

Level of Evidence: C.

9. Serial echocardiograms should be used to monitor changes in heart allograft function in response to anti-rejection therapy.

Level of Evidence: C.

10. In a patient with low-grade acute cellular rejection and hemodynamic compromise, the possibility of AMR should also be entertained (see AMR section).

Level of Evidence: C.

11. Interleukin-2 receptor blockers should not be used to reverse acute cellular rejection.

Level of Evidence: C.

Recommendations for the Treatment of Asymptomatic Acute Cellular Rejection:^{205–207,211–217}

Class I:

1. Severe acute cellular rejection (ISHLT 3R) diagnosed by surveillance EMB should be treated even in the absence of symptoms or evidence of heart allograft dysfunction.

Level of Evidence: C.

2. High dose IV CS should be given for asymptomatic severe (ISHLT 3R) acute cellular rejection.

Level of Evidence: C.

3. Asymptomatic moderate acute cellular rejection (ISHLT 2R) can be treated with either IV or oral CS.

Level of Evidence: C.

4. Adjustment of maintenance immunosuppressive therapy should be done in patients with asymptomatic moderate (ISHLT 2R) or severe (ISHLT 3R) acute cellular rejection. This can include an increase of the dose of current medications, addition of an agent, or conversion to a different maintenance regimen.

Level of Evidence: C.

5. Anti-microbial prophylaxis against opportunistic infections should be administered when high-dose CSs and/or cytolytic therapy are used for treatment of rejection..

Level of Evidence: C.

Class IIa:

1. The performance of a follow-up EMB should be considered 2 to 4 weeks after initiation of therapy for asymptomatic moderate or severe acute cellular rejection.

Level of Evidence: C.

2. Cytolytic immunosuppressive therapy can be considered if there is no histologic resolution of rejection on the follow-up EMB.

Level of Evidence: C.

Table 12 Examples of Therapies for Antibody-Mediated Rejection

Therapeutic modality	Dose	Frequency	Duration
Plasmapheresis	1–2 plasma exchanges	Daily	3–5 days
		Every other day	1–2 weeks
		3 times per week	1–4 weeks
		Once weekly	2–4 weeks
IV Ig	100–1,000 mg/kg	1–3 times per week, often given after each plasmapheresis	1–4 weeks
Rituximab	375 mg/m ²	Once weekly	1–4 weeks

IV Ig, intravenous immunoglobulin.

Based on Grauhan O et al,²²¹ Leech SH et al,²²⁶ Michaels PJ et al,²²⁸ Miller LW et al,²²⁹ Kaczmarek I et al,²²² Takemoto SK et al,⁸⁵ and Bierl C et al.³⁹⁶

3. Asymptomatic mild cellular rejection (ISHLT 1R) does not require treatment in the vast majority of cases.

Level of Evidence: C.

Class IIb:

1. Asymptomatic moderate cellular rejection (ISHLT 2R), especially if occurring later than 12 months after HT, may not require treatment. Close surveillance (clinical, echocardiographic, and follow-up EMB) is strongly suggested if no treatment is administered in this setting.

Level of Evidence: C.

Recommendations for Treatment of Recurrent or Resistant Acute Cellular Rejection:^{218,219}

Class I:

1. For recurrent or CS-resistant acute cellular rejection, cytolytic immunosuppressive therapy with anti-thymocyte antibodies should be considered.

Level of Evidence: C.

2. Maintenance immunosuppression should be re-evaluated in patients with recurrent/resistant HT rejection (see above).

Level of Evidence: C.

3. Frequent surveillance of heart allograft function (eg, by echocardiography) is recommended in patients with recurrent/resistant rejection, even if persistently asymptomatic.

Level of Evidence: C.

Class IIb:

1. Additional approaches that can be considered for recurrent or resistant acute cellular rejection include methotrexate pulse therapy, photopheresis, and total lymphoid irradiation.

Level of Evidence: B.

2. Evaluation of EMB specimens for concomitant antibody-mediated rejection (AMR; see the Recommendations for Treatment of Antibody-Mediated Rejection) and determination of the presence of anti-HLA antibodies in the HT recipient's serum is also suggested.

Level of Evidence: C.

Topic 5: Treatment of Hyperacute and Antibody-Mediated Rejection

Recommendations for the Treatment of Hyperacute Rejection:^{25,220}

Class I:

1. Treatment for hyperacute rejection should be initiated as soon as the diagnosis is made, preferably when the HT recipient is still in the operating room. Treatments that should be considered include (1) high-dose IV CS; (2) plasmapheresis; (3) IV immunoglobulin; (4) cytolytic immunosuppressive therapy; (5) IV CNI (CYA, TAC) and metabolic cycle inhibitors (MMF); (6) IV inotropes and vasopressors; and (7) MCS.

Level of Evidence: C.

1. Intraoperative myocardial EMB should be obtained to confirm the diagnosis of hyperacute heart allograft rejection.

Level of Evidence: C.

Class IIb:

1. Urgent retransplantation may be considered if the above measures do not result in restoration of acceptable heart allograft function, but repeat HT in the setting of hyperacute rejection is associated with high mortality.

Level of Evidence: C.

Recommendations for Treatment of Antibody Mediated Rejection^{85,221–229}:

(See Table 12)

Class IIa:

1. The following treatments can be used to disrupt the immune-mediated injury of the heart allograft in AMR: (1) high-dose IV CS and (2) cytolytic immunosuppressive therapy.

Level of Evidence: C.

2. The following treatments may be used to remove circulating anti-HLA antibodies or decrease their reactivity: (1) plasmapheresis; (2) immune apheresis (immunoadsorption); and (3) IV Ig.

Level of Evidence: C.

3. The following treatments are used to maintain adequate cardiac output and systemic blood pressure: (1) IV inotropes and vasopressors and (2) MCS.

Level of Evidence: C.

4. When AMR is suspected, EMB examination should be expanded to include immunohistochemistry stains for complement split products and possibly antibody.

Level of Evidence: C.

5. Recipient serum should be screened for presence, quantity, and specificity of anti-donor (HLA) antibodies.

Level of Evidence: C.

6. Follow-up EMB should be performed 1 to 4 weeks after initiation of therapy and include immunohistochemistry examination.

Level of Evidence: C.

7. Adjustment of maintenance immunosuppressive therapy may be considered. This can include increase in the dose of current immunosuppressive agent(s), addition of new agent(s), or conversion to different agent(s).

Level of Evidence: C.**Class IIb:**

1. Systemic anti-coagulation may decrease intravascular thrombosis in the heart allograft.

Level of Evidence: C.

2. Emergent retransplantation may be considered if the above measures do not restore acceptable heart allograft function, but outcomes in this situation are unfavorable.

Level of Evidence: C.**Topic 6: Management of Late Acute Rejection**

Recommendation for the Management of Late Acute Rejection:^{230,231}

Class I:

1. Maintenance immunosuppression and the intensity of clinical follow-up should be reevaluated after symptomatic or asymptomatic late acute heart allograft rejection.

Level of Evidence: C.**Class IIa:**

1. After the first year, EMB surveillance (eg, every 4–6 months) for an extended period of time is recommended in patients at higher risk for late acute rejection, to reduce the risk of rejection with hemodynamic compromise, and to reduce the risk of death in African-American recipients.

Level of Evidence: C.

2. Repeated education on the critical importance of adherence to treatment, and early reporting of symptoms contribute to the prevention and early recognition of late acute rejection.

Level of Evidence: C.

3. Patients at low risk for late rejection do not appear to significantly benefit from indefinite EMB surveillance. The usefulness of long-term routine EMB should be evaluated against the risks and the costs of the procedure.

Repeated EMB increase the probability of damage to the TV apparatus and collection of non-diagnostic material.

Level of Evidence: C.

4. In pediatric HT recipients, CAV should be considered in the differential diagnosis of late symptomatic or asymptomatic rejection when heart allograft dysfunction is present. Coronary angiography (and possibly IVUS) should be considered in these patients.

Level of Evidence: C.

5. In pediatric HT recipients, late rejection has negative prognostic implications and may be associated with an increased risk for subsequent development of CAV; consequently, a follow-up coronary angiography may be recommended.

Level of Evidence: C.**Class IIb:**

1. In pediatric HT recipients, withholding treatment for asymptomatic mild-moderate late heart allograft rejection is reasonable but requires close follow-up.

Level of Evidence: C.**Task Force 3: Long-term Care of Heart Transplant Recipients**

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Topic 1: Minimization of Immunosuppression

Recommendations for the Minimization of Immunosuppression:^{159,162,188,232–242}

Class I:

1. CS withdrawal can be successfully achieved 3 to 6 months after HT in many low-risk patients (those without circulating anti-HLA antibodies, non-multiparous women, those without a history of rejection, and older HT recipients).

Level of Evidence: B.

2. Lower levels of CNi in HT recipients should be sought when CNi are used in conjunction with MMF (compared with AZA) because with this combination lower levels are safe and associated with lower rejection rates as well as improved renal function.

Level of Evidence: B.**Class IIa:**

1. A PSI may be substituted for CNi later than 6 months after HT to reduce CNi-related nephrotoxicity and CAV in low-risk recipients.

Level of Evidence: C.

Table 13 Basic Criteria for the Interpretation of Intravascular Ultrasound Measurements After Heart Transplantation

Normal	Abnormal	
Baseline study (4–6 weeks after heart transplantation)	0.25–0.50 mm intimal thickness	Any intimal lesion \geq 0.5 mm suggests donor disease ²⁴⁷
Study 1 year after heart transplantation	No change in intimal thickness	An increase in intimal thickness $>$ 0.5 mm from baseline suggests accelerated CAV associated with adverse outcomes ²⁴⁹

Class IIb:

1. CNI monotherapy with early CS withdrawal may be considered in highly selected individuals. This strategy has been associated with acceptable short-term outcomes in HT recipients.

Level of Evidence: B.

2. In pediatric HT recipients, minimization of immunosuppression by CS withdrawal is common practice and appears safe, with the majority of children being free of CS by 5 years after HT.

Level of Evidence: C.

3. Due to variable pharmacokinetics in children, strategies for minimization of immunosuppression in the pediatric population may require a greater reliance on drug levels monitoring than in adults.

Level of Evidence: C.

4. The use of PSI may be considered in pediatric HT recipients to reduce CAV and nephrotoxicity, but insufficient data are available on the effects of PSI in children.

Level of Evidence: C.

Class III:

1. In HT recipients, substitution of PSI for MMF for the specific purpose of lowering CNI exposure to reduce CNI-related nephrotoxicity is not recommended due to the interaction between CNI and PSI, which enhances CNI nephrotoxicity.

Level of Evidence: C.

2. Substitution of a PSI for MMF earlier than 3 months after HT is not recommended due to a higher risk of rejection as well as delayed wound healing.

Level of Evidence: B.

Topic 2: Management of Neurologic Complications After Heart Transplantation

Recommendations for the Management of Neurologic Complications After Heart Transplantation:^{243–246}

Class I:

1. Management of HT recipients with seizures should include reduction of CNI doses (taking into consideration the risk of inadequate immunosuppression) and correction of hypomagnesemia, if present.

Level of Evidence: C.

2. The occurrence of encephalopathy late after HT should prompt neurologic consultation and imaging to identify possible underlying etiologies.

Level of Evidence: C.

3. Posterior reversible leukoencephalopathy (PRES) in HT recipients should be managed with a reduction of CNI doses or substitution with an alternative CNI.

Level of Evidence: C.

Class IIb:

1. Heart transplant recipients who continue to experience seizures after a reduction in the CNI dose may benefit from CNI withdrawal and substitution with a PSI (SRL, EVL).

Level of Evidence: C.

Topic 3: Cardiac Allograft Vasculopathy

Recommendations for the Diagnosis and Management of Cardiac Allograft Vasculopathy^{155–157,164,247–267}

(See Table 13)

Class I:

1. Primary prevention of CAV in HT recipients should include strict control of cardiovascular risk factors (hypertension, diabetes, hyperlipidemia, smoking, and obesity) as well as strategies for the prevention of CMV infection.

Level of Evidence: C.

2. In HT recipients, statin therapy has been shown to reduce CAV and improve long-term outcomes regardless of lipid levels and should be considered for all HT recipients (adult and pediatric).

Level of Evidence: A.

3. Annual or biannual coronary angiography should be considered to assess the development of CAV. Patients free of CAV at 3 to 5 years after HT, especially those with renal insufficiency, may undergo less frequent invasive evaluation.

Level of Evidence: C.

4. Follow-up coronary angiography is recommended at 6 months after a percutaneous coronary intervention because of high restenosis rates in HT recipients.

Level of Evidence: C.

5. Selective coronary angiography is the investigation of choice for the diagnosis of CAV in pediatric HT recipients. It should be performed at yearly or biannual intervals.

Level of Evidence: C.

Class IIa:

1. A baseline coronary angiogram at 4 to 6 weeks after HT may be considered to exclude donor coronary artery disease.

Level of Evidence: C.

2. IVUS in conjunction with coronary angiography with a baseline study at 4 to 6 weeks and at 1 year after HT is an option to exclude donor coronary artery disease, to detect rapidly progressive CAV, and provide prognostic information.

Level of Evidence: B.

3. In HT recipients with established CAV, the substitution of MMF or AZA with a PSI can be considered.

Level of Evidence: B.

4. A PSI can be used in pediatric HT recipients who develop CAV, but the effect of PSI on the progression of CAV in children is unknown.

Level of Evidence: C.

5. IVUS can be safely used in older pediatric HT recipients to assess CAV.

Level of Evidence: C.

6. Evaluation of coronary flow reserve in conjunction with coronary angiography may be useful for the detection of small-vessel coronary disease, which is a manifestation of CAV.

Level of Evidence: C.

7. Treadmill or dobutamine stress echocardiography and myocardial perfusion imaging may all be useful for the detection of CAV in HT recipients unable to undergo invasive evaluation. Non-invasive testing for CAV is technically possible in children.

Level of Evidence: B.

8. Percutaneous coronary intervention with drug-eluting stents is recommended in both adults and children with CAV and offers short-term palliation for appropriate discrete lesions.

Level of Evidence: C.

9. Surgical revascularization in HT recipients with CAV is an option in highly selected patients who have lesions amenable to surgical revascularization.

Level of Evidence: C.

10. Cardiac retransplantation may be considered in patients with severe CAV and absence of contraindications for repeat HT.

Level of Evidence: C.

Class IIb:

1. Ultrafast computed tomography (CT) for the detection of coronary calcium has been used mostly as an investigational tool for assessing CAV in HT recipients, but is being superseded by advances in CT angiography.

Level of Evidence: C.

2. CT coronary angiography shows promise in the evaluation of CAV in HT recipients, although higher resting heart rates in these patients limit the technical quality of this study.

Level of Evidence: C.

Topic 4: Malignancy After Heart Transplantation**Recommendations on the Approach to Malignancy After Heart Transplantation:**^{268–271}**Class I:**

1. Recommendations regarding screening for breast, colon, and prostate cancer in the general population should also be followed in HT recipients.

Level of Evidence: C.

2. It is recommended that HT recipients have close skin cancer surveillance, including education on preventive measures and yearly dermatologic examinations.

Level of Evidence: C.

3. Initial evaluation and a therapeutic plan for post-transplant lymphoproliferative disorder (PTLD) in HT recipients should be done at the transplant center by physicians familiar with transplant-associated malignancies.

Level of Evidence: C.

4. There is no evidence to support a reduction in immunosuppression in patients with solid tumors unrelated to the lymphoid system. Maintenance immunosuppression should be continued unless there are specific reasons to reduce certain drugs, such as reduction of bone marrow-suppressive agents if leucopenia occurs.

Level of Evidence: C.

Class IIa:

1. Chronic immunosuppression should be minimized in HT recipients as possible, particularly in patients at high risk for malignancy.

Level of Evidence: C.

Topic 5: Chronic Kidney Disease After Heart Transplantation**Recommendations on Chronic Kidney Disease After Heart Transplantation:**^{70,242–244,272–282}**Class I:**

1. Estimation of glomerular filtration rate (GFR) with the modified diet in renal disease (MDRD) equation, urinalysis, and spot urine albumin/creatinine ratio should be obtained at least yearly after HT. Measurement of sCr for estimation of GFR should be obtained more often in patients with GFR < 60 ml/min/1.73 m², and/or fast GFR decline in the past (> 4 ml/min/1.73 m² per year).

Level of Evidence: C.

2. Although in children there is no consensus on the optimal method to estimate GFR, this measurement should be done and a urinalysis obtained at least yearly in pediatric HT recipients.

Level of Evidence: C.

3. Heart transplant recipients with an estimated GFR < 30 ml/min/1.73 m², proteinuria > 500 mg/day (or urine albumin/creatinine ratio > 500 mg/g), or rapidly declining GFR (> 4 ml/min/1.73 m² per year), should be referred to a nephrologist for management of metabolic

abnormalities and other complications of renal insufficiency and consideration of renal transplantation.

Level of Evidence: C.

- In all HT recipients (adult and pediatric) with chronic kidney disease (CKD), CNI exposure should be lowered to the minimum level required for effective immunosuppression. In patients taking AZA, this may be achieved by conversion of AZA to MMF.

Level of Evidence: B.

- Owing to the potential for precipitating rejection, CNI-free regimens should be used with caution in HT recipients with significant renal insufficiency that persists despite CNI reduction.

Level of Evidence: C.

- In pediatric HT recipients, CS minimization or withdrawal should be attempted to avoid hypertension and subsequent CKD, as long as there is no clinical rejection. There are no strong data in adult HT recipients.

Level of Evidence: B.

- Interventions that have been proven to slow the progression of CKD in the general population should be considered in all HT recipients. These include strict glucose and blood pressure control and use of an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB). The American Diabetes Association (ADA) or the International Diabetes Federation Guidelines should be used to manage diabetes. Blood pressure should be treated according to the Joint National Committee VII or the European Society of Cardiology 2007 Guidelines.

Level of Evidence: C.

- In pediatric HT recipients, diabetes is rare. In contrast, hypertension is common, and adequate blood pressure control with a CCB or ACEI is warranted to avoid CKD.

Level of Evidence: C.

- Hemoglobin (Hgb) levels should be measured at least annually in all HT patients with CKD. If anemia (Hgb < 13.5 g/dl in adult men; < 12 g/dl in adult women) is detected, iron status should be addressed and erythropoiesis-stimulating agents should be used to maintain Hgb levels between 11 and 13 g/dl.

Level of Evidence: C.

- Kidney transplantation should be considered the treatment of choice for all HT recipients (adult and pediatric) with end-stage renal disease who are appropriate candidates. Living donation should be considered.

Level of Evidence: C.

Class IIa:

- CCBs should be considered the anti-hypertensive drug of choice when optimal blood pressure control cannot be achieved with ACEI/ARB or when these drugs are contraindicated in HT recipients.

Level of Evidence: C.

Topic 6: Management of Diabetes Mellitus After Heart Transplantation

Recommendations for the Management of Diabetes After HT:²⁸³⁻²⁸⁸

Class I:

- Prevention, early detection, and appropriate therapy for diabetes should be considered as an important component of patient care after HT.

Level of Evidence: C.

- Patients should be periodically screened for diabetes after HT by measuring fasting plasma glucose levels or with an oral glucose tolerance test (more sensitive screening test for pre-diabetic state) and HgbA_{1C} determination, as appropriate. The frequency of screening will depend on risk factors and immunosuppressive therapy.

Level of Evidence: C.

- Therapies for short-term peri-operative and long-term chronic glycemic control in HT recipients should be based on ADA recommendations.

Level of Evidence: C.

- Heart transplant recipients with diabetes should be counseled regarding weight control, diet and nutrition, and exercise.

Level of Evidence: C.

- Pre-HT risk factors should be assessed, and diabetogenic immunosuppressive medications should be minimized whenever possible in HT recipients.

Level of Evidence: C.

- CS-sparing regimens and decreased CNI doses should be used as appropriate to prevent diabetes in HT recipients.

Level of Evidence: C.

- Associated cardiovascular risk factors (in addition to diabetes), such as hyperlipidemia and hypertension, should be managed aggressively in HT recipients. Annual measurements of lipids levels should be performed according to ADA recommendations.

Level of Evidence: C.

- Annual screening should be performed for diabetic complications (ophthalmology, podiatry, peripheral vascular disease, etc) in HT recipients with diabetes.

Level of Evidence: C.

Class IIa:

- An endocrinology consultation may be considered when a pre-diabetic state or diabetes is diagnosed in a HT recipient.

Level of Evidence: C.

Topic 7: Other Complications of Chronic Immunosuppression

Recommendations on the Management of Various Complications of Chronic Immunosuppression²⁸⁹⁻³³³:

(See Table 14)

Class I:

- Recommendations for addressing other complications of immunosuppression include regular screening for adverse events, minimizing drug doses, drug substitu-

Table 14 Complications of Immunosuppressive Drugs

Drug	Toxicities
Calcineurin inhibitors: cyclosporine and tacrolimus	<p><i>Cardiovascular:</i> hypertension, edema³¹¹</p> <p><i>Neurologic:</i> headache, tremor, insomnia, hearing loss posterior reversible encephalopathy syndrome Parkinsonism, central and peripheral neuropathy, seizures^{303–311}</p> <p><i>Hematologic:</i> Anemia, leukopenia, thrombotic microangiopathy, eosinophilia^{294,311,312}</p> <p><i>Dermatologic:</i> fibrovascular polyps alopecia,^{295,313} hirsutism, gingival hyperplasia²⁹⁶</p> <p><i>Gastrointestinal:</i> nausea, diarrhea, steatohepatitis, cholestatic jaundice, colonic malakoplakia, eosinophilic gastroenterocolitis, villous atrophy/food allergies, hepatic veno-occlusive disease^{294,297,311,314–317}</p> <p><i>Endocrine/metabolic:</i> hypophosphatemia, hypomagnesemia, hyperglycemia, hyperkalemia, hyperlipemia³¹¹</p> <p><i>Renal:</i> renal dysfunction/nephropathy³¹¹</p> <p>Infection³¹¹</p>
Mammalian target of rapamycin inhibitors	<p><i>Cardiovascular:</i> edema, hypertension³¹¹</p> <p><i>Neurologic:</i> Headache, progressive multifocal encephalopathy, optic neuropathy^{311,318}</p> <p><i>Hematologic:</i> Anemia, thrombocytopenia, thrombotic microangiopathy, venous thromboses^{298,311,319,320}</p> <p><i>Respiratory:</i> Dyspnea, pulmonary toxicity, interstitial pneumonitis, c, alveolar proteinosis, alveolar hemorrhage^{299,300,311,321,322}</p> <p><i>Endocrine and metabolic:</i> Hypertriglyceridemia, hypercholesterolemia³¹¹</p> <p><i>Dermatologic:</i> Acneiform facial dermatitis, ulcerating rash: perforating collagenosis, wound healing complications: dehiscence, leukocytoclastic vasculitis^{301,323}</p> <p><i>Musculoskeletal:</i> extremity lymphedema (bilateral and unilateral); lingual angioedema; impaired wound healing^{289,324}</p> <p><i>Gastrointestinal:</i> Diarrhea, nausea, vomiting, gastroduodenal ulcer disease; hepatotoxicity^{311,325,326}</p> <p><i>Genitourinary:</i> urinary tract infection, infertility (oligospermia)^{302,311,327}</p> <p><i>Infection</i> (eg, herpes simplex virus and cytomegalovirus)^{291,328,329}</p> <p><i>Gastrointestinal</i> (eg, nausea, constipation, diarrhea, vomiting, dyspepsia, abdominal distension and pain, esophagitis)^{291,328,329}</p> <p><i>Metabolism and nutritional</i> (eg, hyperglycemia, hypercholesterolemia, gout)^{291,311}</p> <p><i>Cardiovascular</i> (eg, hypertension, peripheral edema)^{291,311}</p> <p><i>Hematologic</i> (eg, leukopenia, thrombocytopenia)^{291,311,328}</p> <p><i>Nervous system</i> (eg, headache, tremor)^{291,311}</p> <p><i>Respiratory</i> (eg, dyspnea, respiratory tract infection, cough)²⁹¹</p> <p><i>Renal</i> (eg, increased BUN and/or creatinine)³¹¹</p> <p><i>Dermatologic</i> (eg, rash)³¹¹</p>
Mycophenolate mofetil	<p><i>Gastrointestinal</i> (eg, peptic ulcer, esophagitis, pancreatitis)³¹¹</p> <p><i>Neuromuscular and skeletal</i> (eg, osteoporosis, pathologic fractures, muscle mass loss, CS myopathy)^{311,330–333}</p> <p><i>Central nervous system</i> (eg, emotional instability, headache)³¹¹</p> <p><i>Dermatologic</i> (eg, bruising, thin fragile skin, impaired wound healing)³¹¹</p> <p><i>Endocrine and metabolic derangements</i> (eg, diabetes mellitus, hyperlipidemia, fluid retention, growth suppression in children, adrenal suppression, adrenocortical and pituitary unresponsiveness in times of stress, and menstrual irregularities)³¹¹</p> <p><i>Ocular complications</i> (eg, glaucoma, cataracts)³¹¹</p>
Corticosteroids (CS)	

BOOP, bronchiolitis obliterans with organizing pneumonia; BUN, blood urea nitrogen.

tion, and drug withdrawal (as previously discussed), as well as initiating targeted therapies for a specific complication. For example, anti-hyperuricemic therapy and concurrent risk reduction may be used to prevent recurrent attacks of gout, whereas acquired cataracts require surgical intervention. It is important to assess for contraindications and drug interactions when medically treating complications of immunosuppression.

Level of Evidence: C.

Topic 8: Hypertension After Heart Transplantation

Recommendations on the Management of Hypertension After Heart Transplantation:^{334–339}

Class I:

1. Because anti-hypertensive therapy in HT recipients has benefits similar to those in the general population, hypertension after HT should be treated to achieve the same goals recommended for the general population.

Level of Evidence: C.

2. Lifestyle modifications, including weight loss, low-sodium diet, and exercise are appropriate adjuncts to facilitate control of blood pressure in HT recipients.

Level of Evidence: C.

3. Drug choice for treatment of hypertension in HT recipients is empiric and depends on blood pressure responses. CCBs are most widely used, but ACEI and ARB may be preferred in diabetic recipients, and a 2-drug regimen can include both CCB and ACEI/ARB.

Level of Evidence: C.

4. Modification of risk factors such as diabetes and hyperlipidemia are appropriate as adjunctive treatment for hypertension in HT recipients.

Level of Evidence: C.

5. Appropriate adjustment of immunosuppressive therapy, especially CS weaning, may be helpful in management of hypertension in HT recipients.

Level of Evidence: C.**Class IIa:**

1. Hypertension is common in both adults and children after HT and can be assessed with ambulatory blood pressure monitoring.

Level of Evidence: C.**Topic 9: Prophylaxis for Corticosteroid-Induced Bone Disease****Gaps in Evidence:**

Bisphosphonates continue to suppress bone reabsorption after discontinuation of therapy. It is not known, however, if pre-operative administration of these drugs can prevent the increased bone loss that develops after HT with the introduction of CS.

Gaps in Evidence³⁴⁰:

The predictive role of bone mass density (BMD) measurement for fracture risk is unproven in HT recipients. Although several studies have described a beneficial effect of bisphosphonates and vitamin D analogues on bone density in adult HT recipients, none of these studies has been powered to detect a decrease in fracture rate. In addition, important issues that remain unresolved include which is the optimal bisphosphonate, the route and duration of administration, and whether therapy should be continuous or intermittent. More research is also needed to define appropriate indications for bisphosphonate therapy and the optimal agent, dose, and duration of use in pediatric patients.

The potential role in the HT population of the recombinant human parathyroid hormone (teriparatide), a bone forming agent, and strontium ranelate, the first agent to stimulate bone formation while decreasing reabsorption, deserves investigation.

Recommendations for the Prophylaxis of Corticosteroid-Induced Bone Disease After Heart Transplantation:³⁴¹⁻³⁵¹**Class I:**

1. All adult HT candidates should be screened for pre-existing bone disease, preferably at the time of placement on the waiting list. In adults, baseline BMD should be obtained with a dual energy x-ray absorptiometry (DEXA) scan of the lumbar spine and femoral neck.

Level of Evidence: C.

2. The presence of low BMD or vertebral fractures should prompt evaluation and treatment of correctable secondary causes of osteoporosis, because significant improvement in BMD can be attained during the waiting period for HT. Bisphosphonates should be considered the treatment of choice.

Level of Evidence: C.

3. All HT candidates and recipients should have the recommended daily allowance for calcium (1,000–1,500 mg, depending on age and menopausal status) and vitamin D (400–1,000 IU, or as necessary to maintain serum 25-hydroxyvitamin D levels above 30 ng/ml = 75 nmol/L).

Level of Evidence: C.

4. After HT, regular weight-bearing and muscle-strengthening exercises should be encouraged to reduce the risk of falls and fractures and to increase bone density.

Level of Evidence: B.

5. In pediatric HT recipients, it is important to monitor growth and pubertal development and be alert to the development of signs and symptoms of bone disease.

Level of Evidence: C.

6. Reduction or withdrawal of CS in pediatric HT recipients should be considered in the absence of preceding rejection with close monitoring for clinical rejection.

Level of Evidence: B.

7. After HT, children should be encouraged to increase physical activity; daily intake of calcium with vitamin D through diet or supplements should meet recommendations for age.

Level of Evidence: C.

8. All adult HT recipients should begin anti-resorptive therapy with bisphosphonates immediately after HT and continue it at least throughout the first post-operative year.

Level of Evidence: B.

9. Bisphosphonates can be used to treat bone loss in long-term HT recipients and should be used in addition to calcium and vitamin D.

Level of Evidence: C.

10. In pediatric HT recipients who have not reached bone maturity, bisphosphonates should be restricted to patients with reduction in bone mass density associated with low-trauma fractures or vertebral compression.

Level of Evidence: B.**Class IIa:**

1. It is reasonable to perform spine radiographs in all adult HT candidates to detect existing fractures.

Level of Evidence: C.

2. After the first post-HT year, if glucocorticoids have been discontinued and BMD is relatively normal (T score \geq

1.5), it is reasonable to stop bisphosphonates, while maintaining a high degree of vigilance for osteoporosis.

Level of Evidence: C.

- Proximal femur and lumbar spine BMD should be assessed by DEXA scanning in all adult patients 1 year after HT. Thereafter, annual reassessments are wise in patients receiving CS and/or bisphosphonate therapy. However, it should be kept in mind that increases in BMD with bisphosphonates account for a small fraction of their efficacy in preventing bone fractures. It is reasonable to repeat BMD measurement in 2 years in patients with osteopenia and in 3 years in patients with normal bone density. Any clinical suggestion of fracture should prompt bone radiographs.

Level of Evidence: C.

Class IIb:

- Active metabolites of vitamin D (calcidiol, alfacalcidol, and calcitriol) should not be regarded as the first-line treatment for bone loss after HT. If they are used, frequent monitoring of urine and serum calcium levels is required, because hypercalcemia and hypercalciuria are common and may develop anytime during treatment.

Level of Evidence: B.

Class III:

- Calcitonin should not be used to prevent early bone loss after HT.

Level of Evidence: B.

Topic 10: Reproductive Health After Heart Transplantation

Recommendations on Pregnancy After Heart Transplantation:³⁵²⁻³⁵⁴

Class I:

- A multidisciplinary team, involving specialists in maternal and fetal medicine, cardiology and transplant medicine, anesthesia, neonatology, psychology, genetics, and social services, is important in the care of pregnant HT recipients.

Level of Evidence: C.

- The management plan for pregnant HT recipients should be individualized according to the status of the mother and the allograft she received and is best achieved at the primary transplant institution in collaboration with local or referring physicians.

Level of Evidence: C.

- Individual factors in a HT recipient who wishes to become pregnant should be considered, including the risk of acute rejection and infection, review of concomitant therapy that is potentially toxic or teratogenic, and review of the adequacy of graft function. After careful consideration of these individual factors, patients should be counseled on the risks of pregnancy and pregnancy discouraged if graft dysfunction and significant CAV are expected to preclude a successful outcome.

Level of Evidence: C.

- Pregnancy in a HT recipient should generally not be attempted sooner than 1 year after HT.

Level of Evidence: C.

- In a HT recipient who wishes to become pregnant, baseline tests should be obtained to determine the patient's cardiac status and should include an ECG and echocardiogram (and coronary angiography if not performed within the previous 6 months) with the option of right-heart catheterization and EMB, if clinically indicated.

Level of Evidence: C.

- Baseline assessment of renal and liver function should be obtained in a pregnant HT recipient and frequent monitoring of blood pressure, urine cultures, and surveillance for pre-eclampsia and gestational diabetes should be done.

Level of Evidence: C.

- CNIs and CS should be continued in a pregnant HT recipient, but MMF (class D) should be discontinued.

Level of Evidence: C.

- Blood levels of CNI should be monitored closely during pregnancy due to large fluctuations in levels during the pregnancy-related changes in plasma and interstitial volume and hepatic and renal blood flow.

Level of Evidence: C.

- Frequent surveillance for rejection is imperative in a pregnant HT recipient, although surveillance EMB done under fluoroscopy should be avoided. An EMB under echocardiographic guidance or fluoroscopy with leaded patient draping can be performed if necessary.

Level of Evidence: C.

Class IIb:

- The use of AZA (also class D), as a substitute for MMF, is somewhat controversial, and avoidance of both agents in a pregnant HT recipient should be decided on the basis of the balance of maternal and fetal risk.

Level of Evidence: C.

Class III:

- It is uncertain whether the potential risks of drug exposure for the infant outweigh the benefits of breastfeeding, which is therefore not recommended for HT recipients.

Level of Evidence: C.

Recommendations for Contraception After Heart Transplantation:^{355,356}

Class I:

- Before combination hormonal contraception is prescribed, a HT recipient should be screened for risk factors for a hypercoagulable state (a strong family or personal history of thromboembolic events).

Level of Evidence: C.

- Combined hormonal contraception inhibits the CYP-450 3A4 pathway, and immunosuppressant drug blood levels should be monitored carefully when starting this therapy in HT recipients.

Level of Evidence: C.

- Barrier methods provide inadequate pregnancy protection and should be used as an adjunct to other methods in HT recipients. They should be recommended for all sexually active adolescents for sexually transmitted infection (STI) prevention.

Level of Evidence: B.

Class IIb:

- Intrauterine devices (IUD) have been generally not recommended in HT recipients and, in particular, in nulliparous patients because of the increased risk of IUD expulsion in nulliparous women and because of concerns regarding increased risk of pelvic inflammatory infection and infertility.

Level of Evidence: C.

Class III:

- Depo-medroxyprogesterone acetate has been associated with decreased bone density and, therefore, is not routinely recommended for HT recipients.

Level of Evidence: C.

- Hormonal contraception should not be prescribed in HT recipients who have significant hypertension, known CAV, estrogen-sensitive cancers, or active liver disease.

Level of Evidence: C.

Recommendations for the Management of Sexually Transmitted Infections³⁵⁷:

Class I:

- Clinicians should obtain a confidential sexual history from adolescent HT recipients and may consider routine referral to an adolescent medicine specialist who will provide thorough and confidential reproductive health care.

Level of Evidence: C.

- Sexually active adolescents and adult HT recipients with multiple partners should be advised to undergo screening for STI, including a complete anogenital examination to screen for anogenital warts, molluscum, herpes simplex virus (HSV), or other lesions at an appropriate clinic at regular intervals.

Level of Evidence: C.

- A complaint of genitourinary symptoms or disclosure of high-risk behavior should trigger a full evaluation for STI in HT recipients. Genitourinary symptoms may also be an indication for empiric anti-microbial therapy while awaiting results of STI screening.

Level of Evidence: C.

- The quadrivalent human papillomavirus (HPV) vaccine may prevent persistent HPV infection, cervical and vulvovaginal cancer precursor lesions, and genital warts secondary to HPV types 6, 11, 16, and 18. Women should receive all 3 doses before HT. There is no contraindication to administering the vaccine to women after HT, although no studies have confirmed immunogenicity or efficacy in this population.

Level of Evidence: C.

Recommendations for the Management of Erectile Dysfunction After Heart Transplantation³⁵⁸:

Class I:

- Possible iatrogenic causes of erectile dysfunction (ED) should be identified in HT recipients, and alternative medications should be used where possible.

Level of Evidence: C.

- In HT recipients with ED, use of phosphodiesterase inhibitors can be considered. Concomitant nitrate therapy is contraindicated similarly to the general population.

Level of Evidence: C.

- In HT recipients with ED, consider referral to an ED specialist for possible intra-cavernous injections of prostaglandin E1 if phosphodiesterase inhibitors are ineffective or contraindicated.

Level of Evidence: C.

Topic 11: Exercise and Physical Rehabilitation After Heart Transplantation

Recommendations for Exercise and Physical Rehabilitation After Heart Transplantation³⁵⁹⁻³⁶⁸:

Class I:

- The routine use of cardiac rehabilitation with performance of aerobic exercise training is recommended after HT. The short-term benefits of this approach include improvement in exercise capacity and possible modification of cardiovascular risk factors such as obesity, hypertension, and glucose intolerance. There is currently no information on potential long-term benefits.

Level of Evidence: B.

- Resistance exercise is also strongly encouraged in HT recipients to restore BMD and prevent the adverse effects of CS and CNI therapy on skeletal muscle. Resistance exercise should be additive to other therapies for bone mineral loss and muscle atrophy.

Level of Evidence: B.

Class IIa:

- Exercise should be encouraged after pediatric HT, although no data on the long-term benefits exist. Exercise has been shown to produce short-term improvements in functional capacity and perhaps to decrease obesity-related morbidity. Specific exercise programs should be tailored to the specific needs and co-morbidities of the individual HT recipient.

Level of Evidence: C.

Topic 12: Management of Intercurrent Surgery in Heart Transplant Recipients

Recommendations on the Management of Intercurrent Surgery in Heart Transplant Recipients³⁶⁹:

(See Table 15)

Class I:

Table 15 Conversion of Oral to Intravenous Doses of Immunosuppressive Drugs

Cyclosporine	One-third of oral daily dose either as a continuous infusion over 24 hours, or divided into two 6-hourly infusions twice daily
Tacrolimus	One-fifth of the oral daily dose as a continuous infusion over 24 hours
Mycophenolate mofetil	Same as oral dose
Azathioprine	Same as oral dose

- HT recipients requiring intercurrent surgical procedures should have a full pre-operative assessment in collaboration with the transplant team, particularly in preparation for major procedures requiring general or regional anesthesia.

Level of Evidence: C.

- For many surgical procedures, prophylactic anti-biotic administration is now the norm. Protocols may need modification in HT recipients. Aminoglycoside anti-biotics and erythromycin are best avoided because of the risk of worsening renal dysfunction when used in combination with CYA or TAC.

Level of Evidence: C.

- When needed, blood products used in HT recipients should be leukocyte poor. ABO-incompatible infant HT recipients require specialized blood products and must be discussed with the transplant center.

Level of Evidence: C.

- Anesthesia can be safely induced provided that there is clear understanding that the HT is denervated. The resting heart rate is usually higher in HT recipients. Although most allografts have a resting heart rate of approximately 90 beats/min, some have resting sinus rates as high as 130 beats/min, which do not require treatment. It must be remembered that a relative, symptomatic, bradycardia that requires treatment will not respond to atropine. Isoproterenol infusion and pacing are the usual modes of management of HT bradyarrhythmias. Although uncommon, the likeliest sustained atrial arrhythmia is atrial flutter. Likewise, the denervated heart is super-sensitive to adenosine, and the use of standard doses to treat atrial tachyarrhythmias may result in prolonged asystole. Amiodarone is recommended as the drug of choice for atrial tachyarrhythmias in HT recipients.

Level of Evidence: C.

- Care with fluid balance is important because decreased intravascular volume will exacerbate renal dysfunction, and fluid excess may not be well tolerated by HT recipients. For major surgery, CVP monitoring may be necessary.

Level of Evidence: C.

- Immunosuppression should not be discontinued or omitted without discussion with the HT team. However, it may be prudent to omit the dose of CNI on the morning of surgery to avoid potentiating the detrimental effect of dehydration on renal function. Thereafter, immunosuppression should be continued as normal. If medications cannot be given orally CYA should be given IV (often as a 6-hour infusion every 12 hours or as a continuous infusion over 24 hours) at a third of the daily oral dose; TAC can be given IV at a dose one-fifth of the total daily oral dose over 24 hours; AZA should be given IV once daily at the same dose as that taken orally; MMF can be given IV at the same dose taken orally.

Level of Evidence: C.

Topic 13: Return to Work or School and Occupational Restrictions After Heart Transplantation

Recommendations on Return to Work or School and Occupational Restrictions After Heart Transplantation:³⁷⁰⁻³⁷²

Class IIa:

- Health care providers should know that return to work for HT recipients is possible, and not passively support the sick role of patients.

Level of Evidence: C.

- Return to work should be discussed before HT as the goal of post-operative rehabilitation, and not as an exception.

Level of Evidence: C.

- Patients should be encouraged to maintain their jobs as long as possible before HT because this facilitates return to work after HT.

Level of Evidence: C.

- Short-term and long-term goals for returning to work should be discussed as part of the discharge planning after HT.

Level of Evidence: C.

- An employment specialist (eg, a social worker) should be appointed who can set up a proactive employment atmosphere and facilitate the return to work process after HT.

Level of Evidence: C.

- This employment specialist should (1) perform a formal assessment of the patient's educational backgrounds, skills, beliefs, functional and physical limitations, and former work experiences; (2) formulate a career plan with the patient that may help the patient to enter or rejoin the work force or acquire further vocational training; (3) have knowledge of the job market and collaborate with the HT team in learning which physical limitations of the patient must be taken into account; (4) educate future employers about HT and share insights about an individual patient's abilities and restrictions in view of post-operative rehabilitation.

Level of Evidence: C.

Topic 14: Return to Operating a Vehicle After Heart Transplantation

Recommendations for the Operation of a Vehicle After Heart Transplantation

Class I

1. Assessment and discussion of the ability to drive a motor vehicle should be included in the early follow-up of HT recipients.

Level of Evidence: C.

2. Gate stability, tremor, and other neurologic abnormalities should be assessed before HT recipients obtain permission to drive.

Level of Evidence: C.

3. If symptomatic bradycardia is present after HT, the implantation of a permanent pacemaker should be considered before driving is permissible.

Level of Evidence: C.

4. The absence of severe hypoglycemic events should be ascertained before HT recipients are permitted to drive.

Level of Evidence: C.

5. Occupational driving requires that HT recipients meet their country's requirements for occupational driving.

Level of Evidence: C.

6. A high level of scrutiny is required for HT recipients requesting to pilot an aircraft due to the risk of sudden death associated with CAV.

Level of Evidence: C.

Topic 15: Cardiac Retransplantation

Recommendations for Cardiac Retransplantation:³⁷³⁻³⁷⁵

Class I:

1. Retransplantation is indicated in children with at least moderate systolic heart allograft dysfunction and/or severe diastolic dysfunction and at least moderate CAV.

Level of Evidence: B.

Class IIa:

1. It is reasonable to consider listing for retransplantation those adult HT recipients who develop severe CAV not amenable to medical or surgical therapy and symptoms of heart failure or ischemia.

Level of Evidence: C.

2. It is reasonable to consider listing for retransplantation those HT recipients with heart allograft dysfunction and symptomatic heart failure occurring in the absence of acute rejection.

Level of Evidence: C.

3. It is reasonable to consider retransplantation in children with normal heart allograft function and severe CAV.

Level of Evidence: B.

Class IIb:

1. Patients with severe CAV not amenable to medical or surgical therapy with asymptomatic moderate to severe LV dysfunction may be considered for retransplantation.

Level of Evidence: C.

Class III:

1. Adult and pediatric HT recipients with heart allograft failure due to acute rejection or occurring less than 6 months after the first HT and complicated by hemodynamic compromise are inappropriate candidates for retransplantation.

Level of Evidence: C.

Topic 16: Endocarditis Prophylaxis After Heart Transplantation

Recommendations on Endocarditis Prophylaxis in Heart Transplant Recipients:

Class IIa:

1. There are insufficient data to support specific recommendations for endocarditis prophylaxis in HT recipients. However, these patients are at risk of acquired valvular dysfunction, and the outcome of endocarditis is so poor in HT recipients that the use of anti-biotic prophylaxis for dental procedures is considered reasonable in patients with valvulopathies.

Level of Evidence: C.

Topic 17: Frequency of Routine Tests and Clinic Visits in Heart Transplant Recipients

Recommendation on the Frequency of Routine Tests and Clinic Visits in Heart Transplant Recipients³⁷⁶:

Class IIa:

1. Lifelong follow-up by the transplant center is recommended for HT recipients due to (1) the possibility of acute and/or chronic rejection; (2) the chronic use, toxicity, and drug interactions of immunosuppressants and the associated risks for infection and malignancy; and (3) comorbidities requiring specialized monitoring and management.

Level of Evidence: C.

2. Follow-up for HT recipients should be provided by a multidisciplinary team, including surgeons, cardiologists, nurses, psychologists, social workers, dieticians, and physiotherapists, among many others. Patients and caregivers should recognize that HT requires a life-long commitment to medical care.

Level of Evidence: C.

3. The frequency of follow-up visits for HT recipients will depend on the time since HT and the post-operative clinical course.

Level of Evidence: C.

4. In case of an uneventful recovery, follow-up visits are best scheduled every 7 to 10 days during the first month after HT, then every 14 days during the second month, monthly during the first year, and every 3 to 6 months thereafter.

Level of Evidence: C.

5. The frequency of follow-up should be increased if complications occur, particularly in patients with challenging medical or psychosocial conditions.

Level of Evidence: C.

6. Ancillary services, including home care nursing, cardiac rehabilitation, psychologic support, nutritional planning, or patient support groups may also be used as resources in the follow-up of HT recipients, with the understanding that providers of community health care services must communicate with the clinicians at the transplant center to ensure that the care delivered complies with the HT center's standards.

Level of Evidence: C.

7. Local health professionals should inform the transplant center in the case of the following events: (1) hospitalization for any reason; (2) change in medication, including the addition of any anti-biotic, anti-fungal, or anti-viral therapy for confirmed or presumed infection; (3) hypotension or unexplained drop in systolic blood pressure ≥ 20 mm Hg from baseline; (4) increase in resting heart rate > 10 beats/min over baseline; (5) fever $\geq 101^\circ\text{F}$ (38°C) or any unexplained fever $\geq 100.5^\circ\text{F}$ for ≥ 48 hours (38°C); (6) ≥ 2 -pound weight gain in 1 week (ie, 900 g or more); (7) unexplained weight loss of > 5 pounds (ie, 2.3 kg); (8) elective surgery; (9) increased shortness of breath; (10) pneumonia or any respiratory infection; (11) syncope; (12) chest pain other than musculoskeletal symptoms; (13) decline $> 10\%$ in forced expiratory volume in 1 second; (14) abdominal pain; (15) nausea, vomiting or diarrhea; (16) cerebral vascular event, seizure, or mental status changes.

Level of Evidence: C.

Class I:

1. In addition to routine outpatient follow-up visits, HT recipients should have more prolonged visits every 1 to 2 years for more detailed clinical assessment.

Level of Evidence: B.

2. The purpose of the follow-up visits is to monitor for rejection and screen for adverse events, and may include the following: (1) a complete physical examination; (2) review of the medication and changes to the medication based on the results of the examinations; (3) blood work; (4) echocardiogram; (5) coronary angiography and IVUS (every 1 to 2 years); (6) EMB according to the typical schedule outlined in the chart below; (7) additional education and/or interaction with members of the multidisciplinary team. An example of a typical biopsy schedule for the first year could be:

Biopsy 1, 2, 3, 4, and 5:	Weekly
Biopsy 6, 7, and 8:	Every 14 days
Biopsy 9 and 10:	Every 3 weeks
Biopsy 11, 12, and 13:	Every 4 weeks
Subsequent biopsies during the 1st year after HT:	Every 5 to 6 weeks

This recommendation is addressed in more detail in Task Force 2.

Level of Evidence: B.

3. In pediatric practice, far fewer biopsies are performed due to the need for general anesthesia in small children and the difficulties with venous access and bioptome manipulation in small hearts and vessels. There is no consensus on the frequency of biopsy in children. Some centers do no EMB at all, but instead use detailed echocardiographic assessment. Besides scheduled clinic appointments, the patients should be encouraged to contact the transplant center with questions, concerns, or unexpected symptoms.

Level of Evidence: C.

Topic 18: Psychologic Issues Particularly Related to Adherence to Medical Therapy in Heart Transplant Recipients

Recommendations on Psychologic Issues After Heart Transplantation:³⁷⁷⁻³⁸³

Class IIa:

1. Adherence with the prescribed regimen should be routinely assessed at every HT outpatient clinic visit.

Level of Evidence: C.

2. Because there is currently no gold standard for adherence assessment in HT recipients, it is recommended to combine methods to increase accuracy of assessment (eg, a combination of self-report or parent report in case of children, drug levels assessment, and clinical judgment).

Level of Evidence: C.

3. Attention should be given not only to adherence to the immunosuppressive regimen but also to all other health recommendations appropriate for HT recipients.

Level of Evidence: C.

4. Barriers to adherence should be discussed in an open, non-threatening way during visits with HT recipients.

Level of Evidence: C.

5. Tailored interventions, in close collaboration with the HT recipient and his or her family, should be considered and their efficacy explored. Strategies that seem most effective include offering education repeatedly, reducing the complexity of the medication regimen, providing feedback on a patient's behavior, and combining strategies.

Level of Evidence: C.

6. Strategies to enhance maturity and independence may be particularly helpful in the adolescent HT recipients.

Level of Evidence: C.

7. Because adherence to medical recommendations is a complex issue, health care teams would benefit from training in measuring adherence, discussing its barriers, and implementing adherence-enhancing interventions for HT recipients.

Level of Evidence: C.

8. Each HT center should closely collaborate with a specialized nurse or psychologist who can screen and mon-

itor all HT recipients at risk for non-adherence. Investing in specialized staff may result in better transplant outcomes in the long-term, although further studies testing the efficacy of adherence-enhancing interventions are warranted.

Level of Evidence: C.

9. Depressive symptoms should be regularly evaluated during follow-up of HT recipients. This can best be done by user-friendly, validated screening instruments. All patients with elevated scores should be referred to specialized treatment.

Level of Evidence: C.

10. Each HT team should include a psychologist who is qualified to detect and treat depression. Multidisciplinary treatment teams are better prepared to address psychosocial risk factors for poor outcomes after HT.

Level of Evidence: C.

Class I:

1. Serotonin reuptake inhibitors, particularly citalopram, and new-generation anti-depressants (mirtazapine) may be the best choice for HT recipients because they have no significant impact on blood pressure, heart rate, rhythm, or conduction intervals.

Level of Evidence: B.

2. Agents that interact with the metabolism of CYA and TAC via the CYP450 system (eg, fluvoxamine, nefazodone) should be avoided because they may alter CNI levels.

Level of Evidence: B.

3. Tricyclic anti-depressants (eg, imipramine, desipramine, amitriptyline, and clomipramine) are associated with cardiovascular toxicity (conduction delay, orthostatic hypotension, and anti-cholinergic effects) and may lower seizure thresholds, and therefore, their use should be restricted to HT recipients with severe depression refractory to other therapies. Monoamine oxidase inhibitors (MAOIs) should be avoided because of their hypotensive effects, interactions with anesthetic and pressor agents, and need for dietary restrictions. Herbal medicines such as St. John's wort (*Hypericum perforatum*) can be harmful because it lowers CYA levels.

Level of Evidence: B.

Topic 19: Management of the Transition from Pediatric to Adult Care After Heart Transplantation

Recommendations on the Management of the Transition from Pediatric to Adult Care After Heart Transplantation:

384-386

Class I:

1. Critical milestones to be achieved by pediatric HT recipients before transition to adult care include (1) understanding of and ability to describe the original cause of their organ failure and need for HT (initial education may have been primarily provided to the parents of the

HT recipient, and repetition is necessary to ensure understanding of the clinical condition by the HT recipient; (2) awareness of the long and short-term clinical implications of chronic immunosuppression (infection prevention, cancer surveillance, academic and vocational aspirations); (3) comprehension of the impact of HT status on sexuality and reproductive health (impact of pregnancy, effect of medications on fertility, any potential teratogenicity of medications, role of genetic counseling and genetic risk of disease recurrence in offspring, and increased susceptibility to sexually transmitted disease); (4) demonstration of a sense of responsibility for self-care (knowledge of medications, ability to obtain prescription refills, adherence to medication and office visits schedules, ability to independently communicate with health providers, recognition of symptoms and signs requiring immediate medical attention, and understanding of health care coverage and eligibility requirements).

Level of Evidence: C.

2. Health care providers should simultaneously prepare the parents for the transition from pediatric to adult care by encouraging independence and self-responsibility in the child.

Level of Evidence: C.

3. Practitioners who care for adults should cultivate partnerships with their pediatric colleagues to gain insight into the care of adolescents and the impact of childhood chronic disease on development and management of childhood causes of end-stage organ failure and congenital diseases. Ideal adult site resources also include a dedicated transfer liaison nurse coordinator, a social worker, and a reproductive specialist.

Level of Evidence: C.

Topic 20: Principles of Shared Care After Heart Transplantation

Recommendations on Principles of Shared Care After Heart Transplantation:

Class I:

1. The HT team should ensure that other involved physicians know telephone numbers and electronic mail addresses of the HT team to enable contact at all times and guarantee prompt responses to referring physicians' queries.

Level of Evidence: C.

2. It is helpful for physicians outside the HT team to receive the patient's plan for scheduled HT office visits at the transplant center.

Level of Evidence: C.

3. Formal procedures should be instituted to regularly inform the referring physician of clinical results and medical regimens.

Level of Evidence: C.

ABBREVIATIONS

AAIR = atrium paced, atrium sensed inhibited rate modulation
ACC = American College of Cardiology

ACEI = angiotensin converting enzyme inhibitor	IgG = immunoglobulin G
ACT = activated clotting time	INR = international normalized unit
ADA = American Diabetes Association	ISHLT = International Society for Heart and Lung Transplantation
AHA = American Heart Association	IUD = intrauterine device
AMR = antibody-mediated rejection	IV = intravenous
AP = aerosolized pentamidine	IVUS = intravascular ultrasound
aPTT = activated partial thromboplastin time	LV = left ventricle
ARB = angiotensin receptor blocker	LVEF = left ventricular ejection fraction
ATG = anti-thymocyte globulin	LVH = left ventricular hypertrophy
AZA = azathioprine	MAOI = monoamine oxidase inhibitors
BiV = biventricular	MCS = mechanical circulatory support
BMD = bone mass density	MDRD equation = modified diet in renal disease equation
BNP = brain natriuretic peptide	MMF = mycophenolate mofetil
CAV = cardiac allograft vasculopathy	MPA = mycophenolic acid
CCB = calcium channel blocker	mTOR = mammalian target of rapamycin
CEDIA = cloned enzyme donor immunoassay method	MVO ₂ = mixed venous oxygen
CI = cardiac index	PAWP = pulmonary artery wedge pressure
CKD = chronic kidney disease	PCC = prothrombin plasma concentrates
CO = cardiac output	PFA-100 = platelets function assay 100
CPB = cardiopulmonary bypass	PGF = primary graft failure
CMV = cytomegalovirus	PRA = panel reactive antibodies
CNI = calcineurin inhibitor	PRES = posterior reversible leukoencephalopathy
CRP = C-reactive protein	PSI = proliferation signal inhibitor
CS = corticosteroid	PTLD = posttransplant lymphoproliferative disorder
CT = computed tomography	PT = prothrombin time
CVP = central venous pressure	PTT = partial thromboplastin time
CYA = cyclosporine	PVR = pulmonary vascular resistance
CYP3A = cytochrome P-450 3A4	RAP = right atrial pressure
DDDR = dual-paced, dual-sensed, dual-response to sensing, rate modulation	rFVII = recombinant factor 7
DEXA = dual energy x-ray absorptiometry	RV = right ventricle
DSA = donor specific antibody	sCr = serum creatinine
ECG = electrocardiogram	SRL = sirolimus
ED = erectile dysfunction	STI = sexually transmitted infection
ECMO = extracorporeal membrane oxygenation	SVT = sustained ventricular tachycardia
EMB = endomyocardial biopsy	TAC = tacrolimus
EMIT = enzyme multiplied immunoassay technique	TEE = transesophageal echocardiogram
ESC = European Society of Cardiology	TMP/SMZ = trimethoprim/sulfamethoxazole
EVL = everolimus	TTE = transthoracic echocardiogram
FFP = fresh frozen plasma	TV = tricuspid valve
GFR = glomerular filtration rate	VAD = ventricular assist device
Hgb = hemoglobin	VER = ventricular evoked responses
HIT = heparin-induced thrombocytopenia	VT = ventricular tachycardia
HLA = human leukocyte antigen	
HPLC = high-performance liquid chromatography	
HPV = human papillomavirus	
HRS = Heart Rhythm Society	
HSV = herpes simplex virus	
HT = heart transplant	
ICU = intensive care unit	
Ig = immunoglobulin	

Conflict of Interest Disclosures

Contributing Writers and Reviews

Each writing group member and editorial oversight committee member completed a disclosure form that is maintained on file at the ISHLT headquarters. The conflict of interest disclosures are as follows:

Name	Commercial Interest	Relationship
Allen S. Anderson	XDx	Grant research/support
David A. Baran	XDx	Grant research/support
	Astellas	Grant research/support
	Gilead	Speakers bureau
	GSK	Speakers bureau
	United Therapeutics	Advisory board
Geetha Bhat	Nothing to disclose	

Name	Commercial Interest	Relationship
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	Blue Cross/Blue Shield consultant	
Michael Carboni	Nothing to disclose	
Michael Chan	Nothing to disclose	
Richard Chinnock	Nothing to disclose	
Maria Rosa Costanzo	CHF Solutions	Consultant; speaker
	St. Jude	Speaker; research grant
	Cardiomems	Research grant
	Paracor	Research grant
Marisa Crespo-Leiro	Roche	Research grant/speaker
	Novartis	Research grant/speaker
	Wyeth	Research grant
	Astellas Pharma	Research grant/speaker
Diego Delgado	Astellas	Research grant
	Novartis	Research grant
Reynolds Delgado	Gilead	Speakers bureau
	Eli Lilly	Speakers bureau
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Fabienne Dobbels	Astellas	Speaker/research grant
	BMS	Scientific advisor/research grant
		Speakers bureau
	Novartis	Scientific advisor/speaker
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	Novartis	Consultant/scientific advisor
	Wyeth	Grant/research support
	Wyeth	Scientific medical/advisory
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	Alere	Sci/medical advisory board
	Medtronic	Consultant
	GSK	Speakers bureau
Gonzalo Gonzalez-Stawinski	Thoratec	Honorarium, travel grant
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Jeff Hosenpud	Nothing to disclose	
Sharon Hunt	Nothing to disclose	
Maryl Johnson	CVS (Caremark)	Consultant
Walter Kao	Nothing to disclose	
Anne Keogh	Pfizer	Research grant
	Heartware	Research grant
	Novartis	Research grant
	Bayer	Research grant
	Bayer	Sci/medical advisory board
	GSK	Research grant
	GSK	Sci/medical advisory board
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	Novartis	Research grant
Daniel Kim	Nothing to disclose	
Jon Kobashigawa	Novartis	Research grants

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	Genzyme	Research grant
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	Nothing to disclose	
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	XDX	Honorarium
Gareth Parry Jignesh Patel	Nothing to disclose	
	Novartis	Grant research/support
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	Novartis	Consultant/scientific advisor
	Medtronic	Grant/research support
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	Nothing to disclose	Speaker
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	Nothing to disclose	
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	Astellas	Speaker's bureau
	Wyeth	Grant/research support
	Roche	Research grant
Genzyme	Speakers bureau	
Genzyme	Grant/research support	

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