ELSEVIER

The Journal of
Heart and Lung
Transplantation

http://www.jhltonline.org

SPECIAL FEATURE

The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients

Chair: Maria Rosa Costanzo, MD
Task Force 1: Chair: Maria Rosa Costanzo, MD; *Co-Chairs:* Anne Dipchand, MD; Randall Starling, MD
Contributing Writers: Allen Anderson, MD; Michael Chan, MD; Shashank Desai, MD; Savitri Fedson, MD; Patrick Fisher, MD; Gonzalo Gonzales-Stawinski, MD; Luigi Martinelli, MD; David McGiffin, MD; Francesco Parisi, MD; Jon Smith, MD
Task Force 2: Chair: David Taylor, MD
Co-Chairs: Bruno Meiser, MD; Steven Webber, MD
Contributing Writers: David Baran, MD; Michael Carboni, MD; Thomas Dengler, MD; David Feldman, MD; Maria Frigerio, MD; Abdallah Kfoury, MD; Daniel Kim, MD; Jon Kobashigawa, MD; Michael Shullo, PharmD; Josef Stehlik, MD; Jeffrey Teuteberg, MD; Patricia Uber, PharmD; Andreas Zuckermann, MD
Task Force 3: Chair: Sharon Hunt, MD
Co-Chair: Michael Burch
Contributing Writers: Geetha Bhat, MD; Charles Canter, MD; Richard Chinnock, MD; Marisa Crespo-Leiro, MD; Reynolds Delgado, MD; Fabienne Dobbels, PhD; Kathleen Grady, PhD; Kao W, MD; Jaqueline Lamour, MD; Gareth Parry, MD; Jignesh Patel, MD; Daniela Pini, MD; Sean Pinney, MD; Jeffrey Towbin, MD; Gene Wolfel, MD
Independent Reviewers: Diego Delgado, MD; Howard Eisen, MD; Lee Goldberg, MD; Jeff Hosenpud, MD; Maryl Johnson, MD; Anne Keogh, MD; Clive Lewis, MD; John O'Connell, MD; Joseph Rogers, MD; Heather Ross, MD; Stuart Russell, MD; Johan Vanhaecke, MD

INSTITUTIONAL AFFILIATIONS

Chair: Costanzo MR: Midwest Heart Foundation, Lombard Illinois, USA

Task Force 1: Dipchand A: Hospital for Sick Children, Toronto Ontario, Canada; Starling R: Cleveland Clinic Foundation, Cleveland, Ohio, USA; Anderson A: University of Chicago, Chicago, Illinois, USA; Chan M: University of Alberta, Edmonton, Alberta, Canada; Desai S: Inova Fairfax Hospital, Fairfax, Virginia, USA; Fedson S: University of Chicago, Chicago, Illinois, USA; Fisher P: Ochsner Clinic, New Orleans, Louisiana, USA; Gonzales-Stawinski G: Cleveland Clinic Foundation, Cleveland, Ohio, USA; Martinelli L: Ospedale Niguarda, Milano, Italy; McGiffin D: University of Alabama, Birmingham, Alabama, USA; Parisi F: Ospedale Pediatrico Bambino Gesù, Rome, Italy; Smith J: Freeman Hospital, Newcastle upon Tyne, UK

Task Force 2: Taylor D: Cleveland Clinic Foundation, Cleveland, Ohio, USA; Meiser B: University of Munich/Grosshaden, Munich, Germany; Baran D: Newark Beth Israel Medical Center, Newark, New Jersey, USA; Carboni M: Duke University Medical Center, Durham, North Carolina, USA; Dengler T: University of Hidelberg, Heidelberg, Germany; Feldman D: Minneapolis Heart Institute, Minneapolis, Minnesota, USA; Frigerio M: Ospedale Niguarda, Milano, Italy; Kfoury A: Intermountain Medical Center, Murray, Utah, USA; Kim D: University of Alberta, Edmonton, Alberta, Canada; Kobashigawa J: Cedar-Sinai Heart Institute, Los Angeles, California, USA; Shullo M: University of Pittsburgh, Pittsburgh, Pennsylvania, USA; Stehlik J: University of Utah, Salt Lake City, Utah, USA; Teuteberg J: University of Pittsburgh, Pittsburgh, Pennsylvania, USA; Uber P: University of Maryland, Baltimore, Maryland, USA; Zuckermann A: University of Vienna, Vienna, Austria.

Task Force 3: Hunt S: Stanford University, Palo Alto, California, USA; Burch M: Great Ormond Street Hospital, London, UK; Bhat G: Advocate Christ Medical Center, Oak Lawn, Illinois, USA; Canter C: St. Louis Children Hospital, St. Louis, Missouri, USA; Chinnock R: Loma Linda University Children's Hospital, Loma Linda, California, USA; Crespo-Leiro M: Hospital Universitario A Coruña, La Coruña,

Reprint requests: Amanda W. Rowe, International Society for Heart and Lung Transplantation, 14673 Midway Road, Suite 200, Addison, TX 75001. Telephone: 804-873-2541. Fax: 817-912-1237.
E-mail address: susie.newton@ishlt.org; amanda.rowe@ishlt.org

doi:10.1016/j.healun.2010.05.034

Spain; Delgado R: Texas Heart Institute, Houston, Texas, USA; Dobbels F: Katholieke Universiteit Leuven, Leuven, Belgium; Grady K: Northwestern University, Chicago, Illlinois, USA; Kao W: University of Wisconsin, Madison Wisconsin, USA; Lamour J: Montefiore Medical Center, New York, New York, USA; Parry G: Freeman Hospital, Newcastle upon Tyne, UK; Patel J: Cedar-Sinai Heart Institute, Los Angeles, California, USA; Pini D: Istituto Clinico Humanitas, Rozzano, Italy; Pinney S: Mount Sinai Medical Center, New York, New York, USA; Towbin J: Cincinnati Children's Hospital, Cincinnati, Ohio, USA; Wolfel G: University of Colorado, Denver, Colorado, USA

Independent Reviewers: Delgado D: University of Toronto, Toronto, Ontario, Canada; Eisen H: Drexler University College of Medicine, Philadelphia, Pennsylvania, USA; Goldberg L: University of Pennsylvania, Philadelphia, Pennsylvania, USA; Hosenpud J: Mayo Clinic, Jacksonville, Florida, USA; Johnson M: University of Wisconsin, Madison, Wisconsin, USA; Keogh A: St Vincent Hospital, Sidney, New South Wales, Australia; Lewis C: Papworth Hospital Cambridge, UK; O'Connell J: St. Joseph Hospital, Atlanta, Georgia, USA; Rogers J: Duke University Medical Center, Durham, North Carolina, USA; Ross H: University of Toronto, Toronto, Ontario, Canada; Russell S: Johns Hopkins Hospital, Baltimore, Maryland, USA; Vanhaecke J: University Hospital Gasthuisberg, Leuven, Belgium.

J Heart Lung Transplant 2010;29:914–956

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

Contributing Writers: Allen Anderson, MD; Michael Chan, MD; Shashank Desai, MD; Savitri Fedson, MD; Patrick Fisher, MD; Gonzalo Gonzales-Stawinski, MD; Luigi Martinelli, MD; David McGiffin, MD; Jon Smith, MD

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 recip-

ient operations with hemodynamically destabilizing bleeding. 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 Infection[3]:

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 is 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 μg/kg/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 mcg/kg/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 Times[10]:

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 μg/min, *or*
   b. dobutamine, 1 to 10 μg/kg/min $\pm$ dopamine 1 to 10 μg/kg/min, *or*
   c. isoproterenol, 1 to 10 μg/min $\pm$ dopamine 1 to 10 μg/kg/min, *or*
   d. milrinone, 0.375 to 0.75 μg/kg/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)

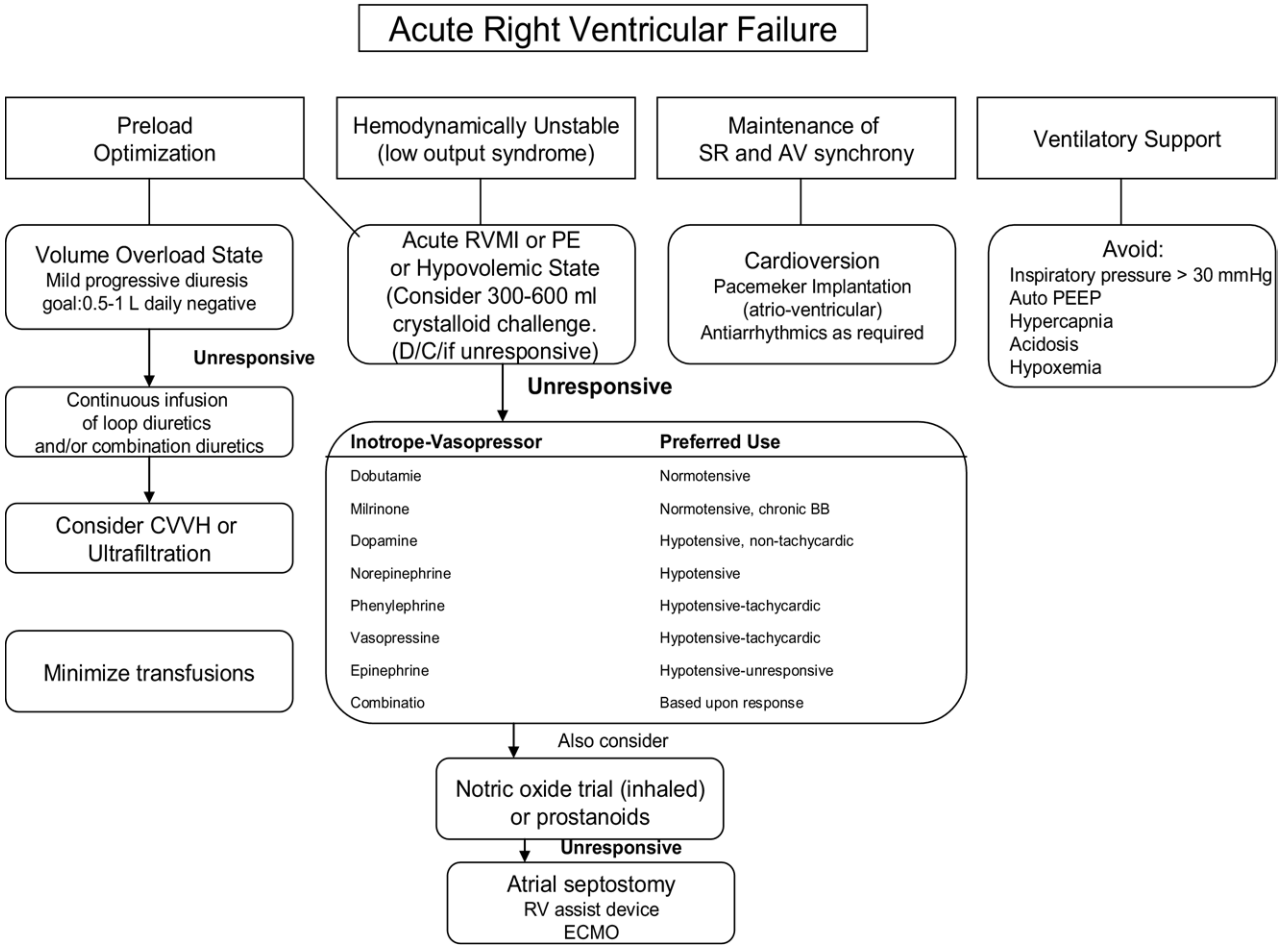

Figure 1 Management of right ventricular dysfunction. AV, atrioventricular; CVVH, continuous venovenous hemofiltration; MI, myocardial infarction; PE, pulmonary embolism; PEEP, positive end-expiratory pressure; SR, sinus rhythm. Adapted and reprinted with permission from Haddad F, et al.[47]

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 cardiopulmonary 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 nephronal 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/Treatment[74]*:*
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 Recipients[75]*:*
(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.
   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.

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 *or* 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 *or* IV ganciclovir (5–10 mg/kg/day) for 1–3 months *or* 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.

Recommendations for Peri-operative Anti-Fungal Prophylaxis in Heart Transplant Recipients[76]*:*
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 Recipients[77]*:*
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	(A) Every 2–4 weeks
	(C) 2–3 g/kg IV divided over 4 days	
	(D) 0.1 mg/kg IV	(D) Every 2–4 weeks
	(E) 100 mg/kg IV	(E) Every 4 weeks
	(F) 20 g (of 10% IV Ig)	
	(G) 150 g (of 10% IV Ig) divided over 3 rounds	(G) Every 4 weeks
Rituximab	(A) 1 g IV	(A) Weekly × 4
	(C, E) 375 mg/m^2	(C) ×2 doses
	(G) 500 mg	(E) Weekly × 4
		(G) Every 2 weeks
Cyclophosphamide (used in the past)	(A) 1 mg/kg orally	(A) Daily
	(C) 0.5 μg/m^2	
	(D) 1 mg/kg orally	

(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 (≥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

	Number of heart transplant centers screening at each interval								
PRA	1 mon	2 mon	3 mon	4–6 mon	1 year	Variable	SE	Other	Total
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]

2. A PRA ≥ 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.
3. The results of the retrospective donor recipient crossmatch may be considered to make decisions regarding immunosuppressive therapy.
   Level of Evidence: C.

Class IIb:

1. 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.
2. 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.
3. 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:

1. 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.
2. In ambulatory, non-sensitized HT candidates it is reasonable to measure anti-HLA antibodies every 6 months.
   Level of Evidence: C.
3. 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.
4. No uniform recommendations exist as to the frequency of anti-HLA antibody determinations after an infection or during MCS.
   Level of Evidence: C.
5. Circulating immunoglobulins should be measured before and after plasmapheresis or immunoabsorption.
   Level of Evidence: C.
6. Lymphocyte sub-populations should be measured before and after the use of rituximab.
   Level of Evidence: C.
7. 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:

1. Initial therapy of AMR can include immunoadsorption and corticosteroid (CS) or plasmapheresis/low dose of IV Ig and CS.
   Level of Evidence: C.
2. Rituximab can be added to reduce the risk of recurrent rejection.
   Level of Evidence: C.
3. 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:

1. 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*

[a]Second 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 Recipients[88–90]**:**
(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 Recipients[92]:

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 intractable or excessive bleeding with HT surgery.
   Level of Evidence: C.

Class III:

1. Although aprotinin can reduce bleeding during HT surgery, 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 because its modest reduction in bleeding has been associated with adverse clinical events.
   Level of Evidence: A.

Topic 6: Documentation and Communication with the Multidisciplinary Team

Recommendations for the Documentation and Communication with the Multidisciplinary Team:[106–108]

Class I:

1. Transplant centers must have a multidisciplinary approach 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 integrated into the patient management team.
   Level of Evidence: B.
2. Transplant centers should strive to have specialty-trained pharmacists or physicians with expertise in pharmacology as part of the multidisciplinary team.
   Level of Evidence: B.

Class IIb:

1. Integration of input from pharmacists and infectious disease 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 recipients 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 Recipients[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 Pediatric Heart Transplant Recipients:[115,116]

Class IIa:

1. The amount of circulatory support provided by ECMO should be sufficient to achieve adequate systemic perfusion and oxygen delivery while waiting for the myocardium to recover.
   Level of Evidence: C.
2. Left heart distension during ECMO support should be aggressively treated because it will compromise pulmonary function and impede LV recovery.
   Level of Evidence: C.

Recommendations for the Timing of Discontinuation of ECMO Support in the Setting of Primary Graft Failure[117]:

Class IIa:

1. Clinical and echocardiographic variables should be serially 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

Chair: David Taylor, MD; *Co-Chairs:* Bruno Meiser, MD; Steven Webber, MD

Contributing Writers: David Baran, MD; Michael Carboni, MD; Thomas Dengler, MD; David Feldman, MD; Maria Frigerio, MD; Abdallah Kfoury, MD; Daniel Kim, MD; Jon Kobashigawa, MD; Michael Shullo, PhD; Josef Stehlik, MD; Jeffrey Teuteberg, MD; Patricia Uber, PharmD; Andreas Zuckermann, MD

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
Nafcillin	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.

[a]Treated-patient population (see text).

[b]Reanalysis 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/mm^3 or absolute total lymphocyte counts $<$ 100 to 200 cells/mm^3.
   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 Recipients[150–210]:

(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.

2. 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.
3. Creatinine kinase levels should be monitored in all children receiving statins.
   Level of Evidence: C.

Class IIa:

1. Calcineurin inhibitor-based therapy remains the standard in immunosuppressive protocols used after HT.
   Level of Evidence: B.
2. 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.
3. 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.
4. 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.
5. Routine use of statins is recommended for all pediatric patients with evidence of hyperlipidemia, CAV, or after retransplantation.
   Level of Evidence: C.
6. 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.
7. 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] > 20 mg not recommended	Myositis (higher)
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 at 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	5 mg/day	5–14 days
Muromonoab-CD3 (OKT3)[b]		

ATG, anti-thymocyte gamma-globulin-fresenius; ATGAM, anti-thymocyte gamma-globulin; IV, intravenous; PO, oral (per os).
[a]Corticosteroid taper can be considered.
[b]Premedicate 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 ascertainment 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

Chair: Sharon Hunt, MD; *Co-Chair:* Michael Burch

Contributing Writers: Geetha Bhat, MD; Charles Canter, MD; Richard Chinnock, MD; Marisa Crespo-Leiro, MD; Reynolds Delgado, MD; Fabienne Dobbels, PhD; Kathleen Grady, PhD; Walter Kao, MD; Jaqueline Lamour, MD; Gareth Parry, MD; Jignesh Patel, MD; Daniela Pini, MD; Jeffrey Towbin, MD; Gene Wolfel, MD

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 ≥ 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 been 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 m^2, and/or fast GFR decline in the past ($>$ 4 ml/min/1.73 m^2 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 m^2, proteinuria $>$ 500 mg/day (or urine albumin/creatinine ratio $>$ 500 mg/g), or rapidly declining GFR ($>$ 4 ml/min/1.73 m^2 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.

4. 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.

5. 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.

6. 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.

7. 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.

8. 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.

9. 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.

10. 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:

1. 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:

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

Level of Evidence: C.

2. 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.

3. 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.

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

Level of Evidence: C.

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

Level of Evidence: C.

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

Level of Evidence: C.

7. 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.

8. 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:

1. 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 Immunosuppression[289–333]**:**
(See Table 14)

Class I:

1. 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	*Cardiovascular:* hypertension, edema[311] *Neurologic:* headache, tremor, insomnia, hearing loss posterior reversible encephalopathy syndrome Parkinsonism, central and peripheral neuropathy, seizures[303–311] *Hematologic:* Anemia, leukopenia, thrombotic microangiopathy, eosinophilia[294,311,312] *Dermatologic:* fibrovascular polyps alopecia,[295,313] hirsutism, gingival hyperplasia[296] *Gastrointestinal:* nausea, diarrhea, steatohepatitis, cholestatic jaundice, colonic malakoplakia, eosinophilic gastroenterocolitis, villous atrophy/food allergies, hepatic veno-occlusive disease[294,297,311,314–317] *Endocrine/metabolic:* hypophosphatemia, hypomagnesemia, hyperglycemia, hyperkalemia, hyperlipemia[311] *Renal:* renal dysfunction/nephropathy[311] Infection[311]
Mammalian target of rapamycin inhibitors	*Cardiovascular:* edema, hypertension[311] *Neurologic:* Headache, progressive multifocal encephalopathy, optic neuropathy[311,318] *Hematologic*: Anemia, thrombocytopenia, thrombotic microangiopathy, venous thromboses[298,311,319,320] *Respiratory:* Dyspnea, pulmonary toxicity, interstitial pneumonitis, c, alveolar proteinosis, alveolar hemorrhage[299,300,311,321,322] *Endocrine and metabolic:* Hypertriglyceridemia, hypercholesterolemia[311] *Dermatologic:* Acneiform facial dermatitis, ulcerating rash: perforating collagenosis, wound healing complications: dehiscence, leukocytoclastic vasculitis[301,323] *Musculoskeletal:* extremity lymphedema (bilateral and unilateral); lingual angioedema; impaired wound healing[289,324] *Gastrointestinal:* Diarrhea, nausea, vomiting, gastroduodenal ulcer disease; hepatotoxicity[311,325,326] *Genitourinary:* urinary tract infection, infertility (oligospermia)[302,311,327]
Mycophenolate mofetil	*Infection* (eg, herpes simplex virus and cytomegalovirus)[291,328,329] *Gastrointestinal* (eg, nausea, constipation, diarrhea, vomiting, dyspepsia, abdominal distension and pain, esophagitis)[291,328,329] *Metabolism and nutritional* (eg, hyperglycemia, hypercholesterolemia, gout)[291,311] *Cardiovascular* (eg, hypertension, peripheral edema)[291,311] *Hematologic* (eg, leukopenia, thrombocytopenia)[291,311,328] *Nervous system* (eg, headache, tremor)[291,311] *Respiratory* (eg, dyspnea, respiratory tract infection, cough)[291] *Renal* (eg, increased BUN and/or creatinine)[311] *Dermatologic* (eg, rash)[311]
Corticosteroids (CS)	*Gastrointestinal* (eg, peptic ulcer, esophagitis, pancreatitis)[311] *Neuromuscular and skeletal* (eg, osteoporosis, pathologic fractures, muscle mass loss, CS myopathy)[311,330–333] *Central nervous system* (eg, emotional instability, headache)[311] *Dermatologic* (eg, bruising, thin fragile skin, impaired wound healing)[311] *Endocrine and metabolic derangements* (eg, diabetes mellitus, hyperlipidemia, fluid retention, growth suppression in children, adrenal suppression, adrenocortical and pituitary unresponsiveness in times of stress, and menstrual irregularities)[311] *Ocular complications* (eg, glaucoma, cataracts)[311]

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 Evidence[340]:

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 ≥

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

3. 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:

1. 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:

1. 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:

1. 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.
2. 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.
3. 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.
4. Pregnancy in a HT recipient should generally not be attempted sooner than 1 year after HT.
Level of Evidence: C.
5. 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.
6. 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.
7. CNIs and CS should be continued in a pregnant HT recipient, but MMF (class D) should be discontinued.
Level of Evidence: C.
8. 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.
9. 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:

1. 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:

1. 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:

1. 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.
2. 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.

3. 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:

1. 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:

1. Depo-medroxyprogesterone acetate has been associated with decreased bone density and, therefore, is not routinely recommended for HT recipients.
   Level of Evidence: C.
2. 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 Infections[357]:
Class I:

1. 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.
2. 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.
3. 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.
4. 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 Transplantation[358]:
Class I:

1. 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.
2. 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.
3. 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 Transplantation:[359–368]
Class I:

1. 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.
2. 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:

1. 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 Recipients[369]:
(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

1. 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.
2. 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.
3. 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.
4. 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.
5. 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.
6. 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:

1. 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.
2. Return to work should be discussed before HT as the goal of post-operative rehabilitation, and not as an exception.
   Level of Evidence: C.
3. 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.
4. 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.
5. 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.
6. 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 Recipients[376]:

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 $\geq$ 20 mm Hg from baseline; (4) increase in resting heart rate $>$ 10 beats/min over baseline; (5) fever $\geq$ 101°F (38°C) or any unexplained fever $\geq$ 100.5° F for $\geq$ 48 hours (38°C); (6) $\geq$ 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
ACT = activated clotting time
ADA = American Diabetes Association
AHA = American Heart Association
AMR = antibody-mediated rejection
AP = aerosolized pentamidine
aPTT = activated partial thromboplastin time
ARB = angiotensin receptor blocker
ATG = anti-thymocyte globulin
AZA = azathioprine
BiV = biventricular
BMD = bone mass density
BNP = brain natriuretic peptide
CAV = cardiac allograft vasculopathy
CCB = calcium channel blocker
CEDIA = cloned enzyme donor immunoassay method
CI = cardiac index
CKD = chronic kidney disease
CO = cardiac output
CPB = cardiopulmonary bypass
CMV = cytomegalovirus
CNI = calcineurin inhibitor
CRP = C-reactive protein
CS = corticosteroid
CT = computed tomography
CVP = central venous pressure
CYA = cyclosporine
CYP3A = cytochrome P-450 3A4
DDDR = dual-paced, dual-sensed, dual-response to sensing, rate modulation
DEXA = dual energy x-ray absorptiometry
DSA = donor specific antibody
ECG = electrocardiogram
ED = erectile dysfunction
ECMO = extracorporeal membrane oxygenation
EMB = endomyocardial biopsy
EMIT = enzyme multiplied immunoassay technique
ESC = European Society of Cardiology
EVL = everolimus
FFP = fresh frozen plasma
GFR = glomerular filtration rate
Hgb = hemoglobin
HIT = heparin-induced thrombocytopenia
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
IgG = immunoglobulin G
INR = international normalized unit
ISHLT = International Society for Heart and Lung Transplantation
IUD = intrauterine device
IV = intravenous
IVUS = intravascular ultrasound
LV = left ventricle
LVEF = left ventricular ejection fraction
LVH = left ventricular hypertrophy
MAOI = monoamine oxidase inhibitors
MCS = mechanical circulatory support
MDRD equation = modified diet in renal disease equation
MMF = mycophenolate mofetil
MPA = mycophenolic acid
mTOR = mammalian target of rapamycin
MVO_2 = mixed venous oxygen
PAWP = pulmonary artery wedge pressure
PCC = prothrombin plasma concentrates
PFA-100 = platelets function assay 100
PGF = primary graft failure
PRA = panel reactive antibodies
PRES = posterior reversible leukoencephalopathy
PSI = proliferation signal inhibitor
PTLD = posttransplant lymphoproliferative disorder
PT = prothrombin time
PTT = partial thromboplastin time
PVR = pulmonary vascular resistance
RAP = right atrial pressure
rFVII = recombinant factor 7
RV = right ventricle
sCr = serum creatinine
SRL = sirolimus
STI = sexually transmitted infection
SVT = sustained ventricular tachycardia
TAC = tacrolimus
TEE = transesophageal echocardiogram
TMP/SMZ = trimethoprim/sulfamethoxazole
TTE = transthoracic echocardiogram
TV = tricuspid valve
VAD = ventricular assist device
VER = ventricular evoked responses
VT = ventricular tachycardia

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
Michael Burch	Novartis	Consultant
Charles Canter	Novartis	Consultant
	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 Lily	Speakers bureau
Thomas Dengler	Nothing to disclose	
Shashank Desai	Nothing to disclose	
Anne Dipchand	Nothing to disclose	
Fabienne Dobbels	Astellas	Speaker/research grant
	BMS	Scientific advisor/research grant Speakers bureau
	Novartis	Scientific advisor/speaker
Howard Eisen	Novartis	Grant/research support
	Novartis	Consultant/scientific advisor
	Wyeth	Grant/research support
	Wyeth	Scientific medical/advisory
Savitri Fedson	Nothing to disclose	
David Feldman	Nothing to disclose	
Patrick Fis her	Nothing to disclose	
Maria Frigerio	Novartis	Speaker
	Genzyme	Speaker
Lee Goldberg	Thoratec	Consultant
	Novartis	Research grant
	Alere	Sci/medical advisory board
	Medtronic	Consultant
	GSK	Speakers bureau
Gonzalo Gonzalez-Stawinski	Thoratec	Honorarium, travel grant
Kathleen Grady	Nothing to disclose	
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
	Actelion	Research grant
	Actelion	Sci/medical advisory board
	Actelion	Speakers bureau
Abdallah Kfoury	XDx	Scientific medical/advisory
	XDx	Grant research/support
	Novartis	Research grant
Daniel Kim	Nothing to disclose	
Jon Kobashigawa	Novartis	Research grants

Name	Commercial Interest	Relationship
	Novartis	Scientific medical/advisory
	XDx	Research grant
	Genzyme	Research grant
Jacqueline Lamour	Nothing to disclose	
Clive Lewis	Roche	Travel grant
	Actelion	Travel grants
Luigi Martinelli	Nothing to disclose	
David McGiffin	Nothing to disclose	
Bruno Meiser	Astellas	Consultant/scientific advisor
John O'Connell	XDX	Honorarium
Gareth Parry	Nothing to disclose	
Jignesh Patel	Novartis	Grant research/support
	QRS Medical Syst.	Sci/med advisory board
Daniela Pini	Nothing to disclose	
Joseph Rogers	Thoratec	Consultant/scientific advisor
Heather Ross	Wyeth	DSMB Member
	Novartis	Principal investigator
Stuart Russell	Thoratec	Consultant
Michael Shullo	Nothing to disclose	
Jon Smith	Nothing to disclose	
Randall Starling	Novartis	Grant/research support
	Novartis	Consultant/scientific advisor
	Medtronic	Grant/research support
	Medtronic	Consultant/scientific advisor
	XDx	Grant research/support
Josef Stehlik	Nothing to disclose	
David Taylor	Nothing to disclose	
Jeffrey Teuteberg	Thoratec Corporation	Consultant
	XDx	Consultant
		Grant research/support
		Speaker
Jeffrey Towbin	PGx Health	Consultant/scientific advisor
	GeneD	Speaker's bureau
Patricia Uber	Geron Corp	Consultant
Steven Webber	Nothing to disclose	
Gene Wolfel	Nothing to disclose	
Andreas Zuckermann	Novartis	Speakers bureau
	Novartis	Consultant/scientific advisor
	Astellas	Speaker's bureau
	Wyeth	Grant/research support
	Roche	Research grant
	Genzyme	Speakers bureau
	Genzyme	Grant/research support

References

1. Young JB, Hauptman PJ, Naftel DC, et al. Determinants of early graft failure following cardiac transplantation, a 10-year, multi-institutional, multivariable analysis. J Heart Lung Transplant 2001;20:212.
2. Lietz K, John R, Mancini DM, Edwards NM. Outcomes in cardiac transplant recipients using allografts from older donors versus mortality on the transplant waiting list; implications for donor selection criteria. J Am Coll Cardiol 2004;43:1553-61.
3. Kubak BM, Gregson AL, Pegues DA, et al. Use of hearts transplanted from donors with severe sepsis and infectious deaths. J Heart Lung Transplant 2009;28:260-5.
4. Brieke A, Krishnamani R, Rocha MJ, et al. Influence of donor cocaine use on outcome after cardiac transplantation: analysis of the United Network for Organ Sharing Thoracic Registry. J Heart Lung Transplant 2008;27:1350-2.
5. De La Zerda DJ, Cohen O, Beygui RE, et al. Alcohol use in donors is a protective factor on recipients' outcome after heart transplantation. Transplantation 2007;83:1214-8.
6. Smith JA, Bergin PJ, Williams TJ, Esmore DS. Successful heart transplantation with cardiac allografts exposed to carbon monoxide poisoning. J Heart Lung Transplant 1992;11:698-700.
7. Snyder JW, Unkle DW, Nathan HM, Yang SL. Successful donation and transplantation of multiple organs from a victim of cyanide poisoning. Transplantation 1993;55:425-7.
8. Navia JL, Atik FA, Marullo A, et al. Bench repair of donor aortic valve with minimal access orthotopic heart transplantation. Ann Thorac Surg 2005;80:313-5.
9. Laks H, Scholl FG, Drinkwater DC, et al. The alternate recipient list for heart transplantation: does it work? J Heart Lung Transplant 1997;16:735-42.
10. Young JB, Naftel DC, Bourge RC, et al. Matching the heart donor and heart transplant recipient. Clues for successful expansion of the donor

pool: a multivariable, multiinstitutional report. The Cardiac Transplant Research Database Group. J Heart Lung Transplant 1994;13:353-64.
11. Blackbourne LH, Tribble CG, Langenburg SE, et al. Successful use of undersized donors for orthotopic heart transplantation—with a caveat. Ann Thorac Surg 1994;57:1472-5.
12. Sethi GK, Lanauze P, Rosado LJ, et al. Clinical significance of weight difference between donor and recipient in heart transplantation. J Thorac Cardiovasc Surg 1993;106:444-8.
13. Bull DA, Stahl RD, McMahan DL, et al. The high risk heart donor: potential pitfalls. J Heart Lung Transplant 1995;14:424-8.
14. Mackintosh AF, Carmichael DJ, Wren C, Cory-Pearce R, English TA. Sinus node function in first three weeks after cardiac transplantation. Br Heart J 1982;48:584-8.
15. Leonelli FM, Pacifico A, Young JB. Frequency and significance of conduction defects early after orthotopic heart transplantation. Am J Cardiol 1994;73:175-9.
16. Leeman M, Van CM, Vachiery JL, Antoine M, Leclerc JL. Determinants of right ventricular failure after heart transplantation. Acta Cardiol 1996;51:441-9.
17. Kimball TR, Witt SA, Daniels SR, Khoury PR, Meyer RA. Frequency and significance of left ventricular thickening in transplanted hearts in children. Am J Cardiol 1996;77:77-80.
18. Mahle WT, Cardis BM, Ketchum D, et al. Reduction in initial ventricular systolic and diastolic velocities after heart transplantation in children: improvement over time identified by tissue Doppler imaging. J Heart Lung Transplant 2006;25:1290-6.
19. Asante-Korang A, Fickey M, Boucek MM, Boucek RJ Jr. Diastolic performance assessed by tissue Doppler after pediatric heart transplantation. J Heart Lung Transplant 2004;23:865-72.
20. Stinson EB, Caves PK, Griepp RB, et al. Hemodynamic observations in the early period after human heart transplantation. J Thorac Cardiovasc Surg 1975;69:264-70.
21. Rothman SA, Jeevanandam V, Combs WG, et al. Eliminating bradyarrhythmias after orthotopic heart transplantation. Circulation 1996; 94(9 suppl):II278-82.
22. Zieroth S, Ross H, Rao V, et al. Permanent pacing after cardiac transplantation in the era of extended donors. J Heart Lung Transplant 2006;25:1142-7.
23. Costanzo-Nordin MR, Liao YL, Grusk BB, et al. Oversizing of donor hearts: beneficial or detrimental? J Heart Lung Transplant 1991;10: 717-30.
24. Minev PA, El-Banayosy A, Minami K, et al. Differential indication for mechanical circulatory support following heart transplantation. Intensive Care Med 2001;27:1321-7.
25. Ibrahim M, Hendry P, Masters R, et al. Management of acute severe perioperative failure of cardiac allografts: a single-centre experience with a review of the literature. Can J Cardiol 2007;23:363-7.
26. Santise G, Petrou M, Pepper JR, et al. Levitronix as a short-term salvage treatment for primary graft failure after heart transplantation. J Heart Lung Transplant 2006;25:495-8.
27. Huang J, Trinkaus K, Huddleston CB, et al. Risk factors for primary graft failure after pediatric cardiac transplantation: importance of recipient and donor characteristics. J Heart Lung Transplant 2004;23: 716-22.
28. Mehra MR, Kobashigawa J, Starling R, et al. Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates—2006. J Heart Lung Transplant 2006;25:1024–2.
29. Bhatia SJ, Kirshenbaum JM, Shemin RJ, et al. Time course of resolution of pulmonary hypertension and right ventricular remodeling after orthotopic cardiac transplantation. Circulation 1987;76:819-26.
30. Stobierska-Dzierzek B, Awad H, Michler RE. The evolving management of acute right-sided heart failure in cardiac transplant recipients. J Am Coll Cardiol 2001;38:923-31.
31. Kieler-Jensen N, Lundin S, Ricksten SE. Vasodilator therapy after heart transplantation: effects of inhaled nitric oxide and intravenous prostacyclin, prostaglandin E1, and sodium nitroprusside. J Heart Lung Transplant 1995;14:436-43.
32. Jeevanandam V, Russell H, Mather P, et al. Donor tricuspid annuloplasty during orthotopic heart transplantation: long-term results of a prospective controlled study. Ann Thorac Surg 2006;82:2089-95.
33. Wong RC, Abrahams Z, Hanna M, et al. Tricuspid regurgitation after cardiac transplantation: an old problem revisited. J Heart Lung Transplant 2008;27:247-52.
34. Hauptman PJ, Couper GS, Aranki SF, et al. Pericardial effusions after cardiac transplantation. J Am Coll Cardiol 1994;23:1625-9.
35. Quin JA, Tauriainen MP, Huber LM, et al. Predictors of pericardial effusion after orthotopic heart transplantation. J Thorac Cardiovasc Surg 2002;124:979-83.
36. Chen EP, Bittner HB, Davis RD, Van TP. Hemodynamic and inotropic effects of milrinone after heart transplantation in the setting of recipient pulmonary hypertension. J Heart Lung Transplant 1998;17: 669-78.
37. Leyh RG, Kofidis T, Struber M, et al. Methylene blue: the drug of choice for catecholamine-refractory vasoplegia after cardiopulmonary bypass? J Thorac Cardiovasc Surg 2003;125:1426-31.
38. Argenziano M, Choudhri AF, Oz MC, et al. A prospective randomized trial of arginine vasopressin in the treatment of vasodilatory shock after left ventricular assist device placement. Circulation 1997; 96(9 suppl):II-90.
39. Morales DL, Garrido MJ, Madigan JD, et al. A double-blind randomized trial: prophylactic vasopressin reduces hypotension after cardiopulmonary bypass. Ann Thorac Surg 2003;75:926-30.
40. Armitage JM, Hardesty RL, Griffith BP. Prostaglandin E1: an effective treatment of right heart failure after orthotopic heart transplantation. J Heart Transplant 1987;6:348-51.
41. Pascual JM, Fiorelli AI, Bellotti GM, Stolf NA, Jatene AD. Prostacyclin in the management of pulmonary hypertension after heart transplantation. J Heart Transplant 1990;9:644-51.
42. Theodoraki K, Tsiapras D, Tsourelis L, et al. Inhaled iloprost in eight heart transplant recipients presenting with post-bypass acute right ventricular dysfunction. Acta Anaesthesiol Scand 2006;50:1213-7.
43. Ardehali A, Hughes K, Sadeghi A, et al. Inhaled nitric oxide for pulmonary hypertension after heart transplantation. Transplantation 2001;72:638-41.
44. Auler Junior JO, Carmona MJ, Bocchi EA, et al. Low doses of inhaled nitric oxide in heart transplant recipients. J Heart Lung Transplant 1996;15:443-50.
45. De Santo LS, Mastroianni C, Romano G, et al. Role of sildenafil in acute posttransplant right ventricular dysfunction: successful experience in 13 consecutive patients. Transplant Proc 2008;40:2015-8.
46. Kirklin JK, Young JB, McGiffin DC. Heart transplantation. Philadelphia: Churchill Livingstone, 2002.
47. Haddad F, Hunt SA, Rosenthal DN, Murphy DJ. Right ventricular function in cardiovascular disease, part I: anatomy, physiology, aging, and functional assessment of the right ventricle. Circulation 2008;117:1436-48.
48. Arafa OE, Geiran OR, Andersen K, et al. Intraaortic balloon pumping for predominantly right ventricular failure after heart transplantation. Ann Thorac Surg 2000;70:1587-93.
49. Jurmann MJ, Wahlers T, Coppola R, Fieguth HG, Haverich A. Early graft failure after heart transplantation: management by extracorporeal circulatory assist and retransplantation. J Heart Transplant 1989; 8:474-8.
50. Tenderich G, Koerner MM, Stuettgen B, et al. Mechanical circulatory support after orthotopic heart transplantation. Int J Artif Organs 1998;21:414-6.
51. Barnard SP, Hasan A, Forty J, Hilton CJ, Dark JH. Mechanical ventricular assistance for the failing right ventricle after cardiac transplantation. Eur J Cardiothorac Surg 1995;9:297-9.
52. Chen JM, Levin HR, Rose EA, et al. Experience with right ventricular assist devices for perioperative right-sided circulatory failure. Ann Thorac Surg 1996;61:305-10.
53. Costard-Jackle A, Fowler MB. Influence of preoperative pulmonary artery pressure on mortality after heart transplantation: testing of potential reversibility of pulmonary hypertension with nitroprusside is useful in defining a high risk group. J Am Coll Cardiol 1992;19:48-54.

54. Bourge RC, Naftel DC, Costanzo-Nordin MR, et al. Pretransplantation risk factors for death after heart transplantation: a multiinstitutional study. The Transplant Cardiologists Research Database Group. J Heart Lung Transplant 1993;12:549-62.
55. Chen JM, Levin HR, Michler RE, et al. Reevaluating the significance of pulmonary hypertension before cardiac transplantation: determination of optimal thresholds and quantification of the effect of reversibility on perioperative mortality. J Thorac Cardiovasc Surg 1997;114:627-34.
56. Erickson KW, Costanzo-Nordin MR, O'Sullivan EJ, et al. Influence of preoperative transpulmonary gradient on late mortality after orthotopic heart transplantation. J Heart Transplant 1990;9:526-37.
57. Bando K, Konishi H, Komatsu K, et al. Improved survival following pediatric cardiac transplantation in high-risk patients. Circulation 1993;88:II218-23.
58. Bauer J, Dapper F, Demirakca S, et al. Perioperative management of pulmonary hypertension after heart transplantation in childhood. J Heart Lung Transplant 1997;16:1238-47.
59. Addonizio LJ, Gersony WM, Robbins RC, et al. Elevated pulmonary vascular resistance and cardiac transplantation. Circulation 1987;76: V52-5.
60. Bailey LL, Gundry SR, Razzouk AJ, et al. Bless the babies: one hundred fifteen late survivors of heart transplantation during the first year of life. The Loma Linda University Pediatric Heart Transplant Group. J Thorac Cardiovasc Surg 1993;105:805-14.
61. Stecker EC, Strelich KR, Chugh SS, Crispell K, McAnulty JH. Arrhythmias after orthotopic heart transplantation. J Card Fail 2005;11: 464-72.
62. Gao SZ, Hunt SA, Wiederhold V, Schroeder JS. Characteristics of serial electrocardiograms in heart transplant recipients. Am Heart J 1991;122:771-4.
63. Holt ND, McComb JM. Cardiac transplantation and pacemakers: when and what to implant. Card Electrophysiol Rev 2002;6:140-51.
64. Miyamoto Y, Curtiss EI, Kormos RL, et al. Bradyarrhythmia after heart transplantation. Incidence, time course, and outcome. Circulation 1990;82(5 Suppl):IV313-7.
65. Pavri BB, O'Nunain SS, Newell JB, Ruskin JN, William G. Prevalence and prognostic significance of atrial arrhythmias after orthotopic cardiac transplantation. J Am Coll Cardiol 1995;25:1673-80.
66. Vaseghi M, Boyle NG, Kedia R, et al. Supraventricular tachycardia after orthotopic cardiac transplantation. J Am Coll Cardiol 2008;51: 2241-9.
67. Ellenbogen KA, Thames MD, DiMarco JP, Sheehan H, Lerman BB. Electrophysiological effects of adenosine in the transplanted human heart. Evidence of supersensitivity. Circulation 1990;81:821-8.
68. Rubel JR, Milford EL, McKay DB, Jarcho JA. Renal insufficiency and end-stage renal disease in the heart transplant population. J Heart Lung Transplant 2004;23:289-300.
69. Costanzo MR, Guglin ME, Saltzberg MT, et al. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. J Am Coll Cardiol 2007;49:675-83.
70. Boyle JM, Moualla S, Arrigain S, et al. Risks and outcomes of acute kidney injury requiring dialysis after cardiac transplantation. Am J Kidney Dis 2006;48:787-96.
71. Anselm A, Cantarovich M, Davies R, Grenon J, Haddad H. Prolonged basiliximab use as an alternative to calcineurin inhibition to allow renal recovery late after heart transplantation. J Heart Lung Transplant 2008;27:1043-5.
72. Furnary AP, Gao G, Grunkemeier GL, et al. Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. J Thorac Cardiovasc Surg 2003;125: 1007-21.
73. Wilson M, Weinreb J, Hoo GW. Intensive insulin therapy in critical care: a review of 12 protocols. Diabetes Care 2007;30:1005-11.
74. Hawkins JA, Breinholt JP, Lambert LM, et al. Class I and class II anti-HLA antibodies after implantation of cryopreserved allograft material in pediatric patients. J Thorac Cardiovasc Surg 2000;119: 324-30.
75. Pagani FD, Dyke DB, Wright S, Cody R, Aaronson KD. Development of anti-major histocompatibility complex class I or II antibodies following left ventricular assist device implantation: effects on subsequent allograft rejection and survival. J Heart Lung Transplant 2001;20:646-53.
76. Feingold B, Bowman P, Zeevi A, et al. Survival in allosensitized children after listing for cardiac transplantation. J Heart Lung Transplant 2007;26:565–1.
77. Pollack-BarZiv SM, den Hollander N, Ngan B-Y, et al. Pediatric heart transplantation in HLA-sensitized patients: evolving management and assessment of intermediate-term outcomes in a high-risk population. Circulation 2007;116(11 suppl):172-8.
78. Betkowski AS, Graff R, Chen JJ, Hauptman PJ. Panel-reactive antibody screening practices prior to heart transplantation. J Heart Lung Transplant 2002;21:644-50.
79. Tambur AR, Pamboukian SV, Costanzo MR, et al. The presence of HLA-directed antibodies after heart transplantation is associated with poor allograft outcome. Transplantation 2005;80:1019-25.
80. Kobashigawa J, Mehra M, West L, et al. Report from a consensus conference on the sensitized patient awaiting heart transplantation. J Heart Lung Transplant 2009;28:213-25.
81. Gebel HM, Bray RA, Nickerson P. Pre-transplant assessment of donor-reactive, HLA-specific antibodies in renal transplantation: contraindication vs. risk. Am J Transplant 2003;3:1488-500.
82. Zangwill S, Ellis T, Stendahl G, et al. Practical application of the virtual crossmatch. Pediatr Transplant 2007;11:650-4.
83. Pei R, Lee JH, Shih NJ, Chen M, Terasaki PI. Single human leukocyte antigen flow cytometry beads for accurate identification of human leukocyte antigen antibody specificities. Transplantation 2003; 75:43-9.
84. Vaidya S. Clinical importance of anti-human leukocyte antigen-specific antibody concentration in performing calculated panel reactive antibody and virtual crossmatches. Transplantation 2008;85:1046-50.
85. Takemoto SK, Zeevi A, Feng S, et al. National conference to assess antibody-mediated rejection in solid organ transplantation. Am J Transplant 2004;4:1033-41.
86. Pisani BA, Mullen GM, Malinowska K, et al. Plasmapheresis with intravenous immunoglobulin G is effective in patients with elevated panel reactive antibody prior to cardiac transplantation. J Heart Lung Transplant 1999;18:701-6.
87. Holt DB, Lublin DM, Phelan DL, et al. Mortality and morbidity in pre-sensitized pediatric heart transplant recipients with a positive donor crossmatch utilizing peri-operative plasmapheresis and cytolytic therapy. J Heart Lung Transplant 2007;26:876-82.
88. West LJ, Pollock-Barziv SM, Dipchand AI, et al. ABO-incompatible heart transplantation in infants. N Engl J Med 2001;344:793-800.
89. Roche SL, Burch M, O'Sullivan J, et al. Multicenter experience of ABO-incompatible pediatric cardiac transplantation. Am J Transplant 2008;8:208-15.
90. West LJ, Karamlou T, Dipchand AI, et al. Impact on outcomes after listing and transplantation, of a strategy to accept ABO blood group-incompatible donor hearts for neonates and infants. J Thorac Cardiovasc Surg 2006;131:455-61.
91. Dipchand AI, Benson L, McCrindle BW, Coles J, West L. Mycophenolate mofetil in pediatric heart transplant recipients: a single-center experience. Pediatr Transplant 2001;5:112-8.
92. Chee YL, Crawford JC, Watson HG, Greaves M. Guidelines on the assessment of bleeding risk prior to surgery or invasive procedures. British Committee for Standards in Haematology. Br J Haematol 2008;140:496-504.
93. Hirsh J. Reversal of the anticoagulant effects of warfarin by vitamin K1. Chest 1998;114:1505-8.
94. Hanley JP. Warfarin reversal. J Clin Pathol 2004;57:1132-9.
95. Leissinger CA, Blatt PM, Hoots WK, Ewenstein B. Role of prothrombin complex concentrates in reversing warfarin anticoagulation: a review of the literature. Am J Hematol 2008;83:137-43.
96. Schulman S, Bijsterveld NR. Anticoagulants and their reversal. Transfus Med Rev 2007;21:37-48.
97. Warkentin TE, Greinacher A, Koster A, Lincoff AM. Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. 8th ed. Chest 2008;133(6 suppl):340-80S.

98. Selleng S, Haneya A, Hirt S, et al. Management of anticoagulation in patients with subacute heparin-induced thrombocytopenia scheduled for heart transplantation. Blood 2008;112:4024-7.
99. Pamboukian SV, Ignaszewski AP, Ross HJ. Management strategies for heparin-induced thrombocytopenia in heart-transplant candidates: case report and review of the literature. J Heart Lung Transplant 2000;19:810-4.
100. Laupacis A, Fergusson D. Drugs to minimize perioperative blood loss in cardiac surgery: meta-analyses using perioperative blood transfusion as the outcome. The International Study of Perioperative Transfusion (ISPOT) Investigators. Anesth Analg 1997;85:1258-67.
101. Karkouti K, Beattie WS, Dattilo KM, et al. A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery. Transfusion (Paris) 2006;46:327-38.
102. Mahdy AM, Webster NR. Perioperative systemic haemostatic agents. Br J Anaesth 2004;93:842-58.
103. Reid RW, Zimmerman AA, Laussen PC, et al. The efficacy of tranexamic acid versus placebo in decreasing blood loss in pediatric patients undergoing repeat cardiac surgery. Anesth Analg 1997;84: 990-6.
104. Levi M, Cromheecke ME, de JE, et al. Pharmacological strategies to decrease excessive blood loss in cardiac surgery: a meta-analysis of clinically relevant endpoints. Lancet 1999;354:1940-7.
105. Cattaneo M, Harris AS, Stromberg U, Mannucci PM. The effect of desmopressin on reducing blood loss in cardiac surgery—a meta-analysis of double-blind, placebo-controlled trials. Thromb Haemost 1995;74:1064-70.
106. Steinman TI, Becker BN, Frost AE, et al. Guidelines for the referral and management of patients eligible for solid organ transplantation. Transplantation 2001;71:1189-204.
107. Dobbels F, Vanhaecke J, Desmyttere A, et al. Prevalence and correlates of self-reported pretransplant nonadherence with medication in heart, liver, and lung transplant candidates. Transplantation 2005;79: 1588-95.
108. Martin JE, Zavala EY. The expanding role of the transplant pharmacist in the multidisciplinary practice of transplantation. Clin Transplant 2004;18(suppl 12):50-4.
109. Canter C, Naftel D, Caldwell R, et al. Survival and risk factors for death after cardiac transplantation in infants. A multi-institutional study. The Pediatric Heart Transplant Study. Circulation 1997;96: 227-31.
110. Frazier EA, Naftel D, Canter C, et al. Death after cardiac transplantation in children: who dies, when, and why. J Heart Lung Transplant 1999;18:69-70.
111. Kirshbom PM, Bridges ND, Myung RJ, et al. Use of extracorporeal membrane oxygenation in pediatric thoracic organ transplantation. J Thorac Cardiovasc Surg 2002;123:130-6.
112. Fenton KN, Webber SA, Danford DA, et al. Long-term survival after pediatric cardiac transplantation and postoperative ECMO support. Ann Thorac Surg 2003;76:843-6.
113. Mitchell MB, Campbell DN, Bielefeld MR, Doremus T. Utility of extracorporeal membrane oxygenation for early graft failure following heart transplantation in infancy. J Heart Lung Transplant 2000; 19:834-9.
114. Huddleston CB, Thul JM. Postoperative management: early graft failure, pulmonary hypertension, and initial immunosuppression strategies (Chapter 7). In: Canter CE, Kirklin JK, editors. ISHLT monograph series volume 2: pediatric heart transplantation. Addison, TX: ISHLT; 2007.
115. Duncan BW. Pediatric mechanical circulatory support. ASAIO J 2005;51:ix-xiv.
116. Seib PM, Faulkner SC, Erickson CC, et al. Blade and balloon atrial septostomy for left heart decompression in patients with severe ventricular dysfunction on extracorporeal membrane oxygenation. Catheter Cardiovasc Interv 1999;46:179-86.
117. Fiser SM, Tribble CG, Kaza AK, et al. When to discontinue extracorporeal membrane oxygenation for postcardiotomy support. Ann Thorac Surg 2001;71:210-4.
118. Cooper LT, Baughman KL, Feldman AM, et al. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology. J Am Coll Cardiol 2007;50:1914-31.
119. Stehlik J, Starling RC, Movsesian MA, et al. Utility of long-term surveillance endomyocardial biopsy: a multi-institutional analysis. J Heart Lung Transplant 2006;25:1402-9.
120. Rosenthal DN, Chin C, Nishimura K, et al. Identifying cardiac transplant rejection in children: diagnostic utility of echocardiography, right heart catheterization and endomyocardial biopsy data. J Heart Lung Transplant 2004;23:323-9.
121. Kemkes BM, Schutz A, Engelhardt M, Brandl U, Breuer M. Noninvasive methods of rejection diagnosis after heart transplantation. J Heart Lung Transplant 1992;11:S221-31.
122. Horenstein MS, Idriss SF, Hamilton RM, et al. Efficacy of signal-averaged electrocardiography in the young orthotopic heart transplant patient to detect allograft rejection. Pediatr Cardiol 2006;27:589-93.
123. Schweiger M, Wasler A, Prenner G, et al. The prognostic validity of the ventricular evoked response (VER) signals in cardiac transplantation. J Heart Lung Transplant 2005;24:1730-5.
124. Butler CR, Thompson R, Haykowsky M, Toma M, Paterson I. Cardiovascular magnetic resonance in the diagnosis of acute heart transplant rejection: a review. J Cardiovasc Magn Reson 2009;11:7.
125. Marie PY, Angioi M, Carteaux JP, et al. Detection and prediction of acute heart transplant rejection with the myocardial T2 determination provided by a black-blood magnetic resonance imaging sequence. J Am Coll Cardiol 2001;37:825-31.
126. Geiger M, Harake D, Halnon N, Alejos JC, Levi DS. Screening for rejection in symptomatic pediatric heart transplant recipients: the sensitivity of BNP. Pediatr Transplant 2008;12:563-9.
127. Dengler TJ, Zimmermann R, Braun K, et al. Elevated serum concentrations of cardiac troponin T in acute allograft rejection after human heart transplantation. J Am Coll Cardiol 1998;32:405-12.
128. Arora S, Gullestad L, Wergeland R, et al. Probrain natriuretic peptide and C-reactive protein as markers of acute rejection, allograft vasculopathy, and mortality in heart transplantation. Transplantation 2007; 83:1308-15.
129. Dengler TJ, Gleissner CA, Klingenberg R, et al. Biomarkers after heart transplantation: nongenomic. Heart Fail Clin 2007;3:69-81.
130. Azzawi M, Hasleton PS, Turner DM, et al. Tumor necrosis factor-alpha gene polymorphism and death due to acute cellular rejection in a subgroup of heart transplant recipients. Hum Immunol 2001;62: 140-2.
131. Keslar K, Rodriguez ER, Tan CD, Starling RC, Heeger PS. Complement gene expression in human cardiac allograft biopsies as a correlate of histologic grade of injury. Transplantation 2008;86:1319-21.
132. Deng MC, Eisen HJ, Mehra MR, et al. Noninvasive discrimination of rejection in cardiac allograft recipients using gene expression profiling. Am J Transplant 2006;6:150-60.
133. Pham MX, Teuteberg JJ, Kfoury AG, et al. Gene-expression profiling for rejection surveillance after cardiac transplantation. N Engl J Med 2010;362:1890-900
134. Rossano JW, Denfield SW, Kim JJ, et al. B-type natriuretic peptide is a sensitive screening test for acute rejection in pediatric heart transplant patients. J Heart Lung Transplant 2008;27:649-54.
135. Bennhagen RG, Sornmo L, Pahlm O, Pesonen E. Serial signal-averaged electrocardiography in children after cardiac transplantation. Pediatr Transplant 2005;9:773-9.
136. Lindenfeld J, Miller GG, Shakar SF, et al. Drug therapy in the heart transplant recipient: part II: immunosuppressive drugs. Circulation 2004;110:3858-65.
137. Cantarovich M, Ross H, Arizon JM, et al. Benefit of Neoral C2 monitoring in de novo cardiac transplant recipients receiving basiliximab induction. Transplantation 2008;85:992-9.
138. Barnard JB, Thekkudan J, Richardson S, et al. Cyclosporine profiling with C2 and C0 monitoring improves outcomes after heart transplantation. J Heart Lung Transplant 2006;25:564-8.
139. Langers P, Press RR, den HJ, et al. Flexible limited sampling model for monitoring tacrolimus in stable patients having undergone liver

transplantation with samples 4 to 6 hours after dosing is superior to trough concentration. Ther Drug Monit 2008;30:456-61.
140. Tsunoda SM, Aweeka FT. Drug concentration monitoring of immunosuppressive agents: focus on tacrolimus, mycophenolate mofetil and sirolimus. BioDrugs 2000;14:355-69.
141. Knight SR, Morris PJ. Does the evidence support the use of mycophenolate mofetil therapeutic drug monitoring in clinical practice? A systematic review. Transplantation 2008;85:1675-85.
142. Stenton SB, Partovi N, Ensom MH. Sirolimus: the evidence for clinical pharmacokinetic monitoring. Clin Pharmacokinet 2005;44:769-86.
143. Brandhorst G, Tenderich G, Zittermann A, et al. Everolimus exposure in cardiac transplant recipients is influenced by concomitant calcineurin inhibitor. Ther Drug Monit 2008;30:113-6.
144. Krasinskas AM, Kreisel D, Acker MA, et al. CD3 monitoring of antithymocyte globulin therapy in thoracic organ transplantation. Transplantation 2002;73:1339-41.
145. Uber PA, Mehra MR, Park MH, Scott RL. Clopidogrel and rhabdomyolysis after heart transplantation. J Heart Lung Transplant 2003; 22:107-8.
146. Hmiel SP, Canter C, Shepherd R, Lassa-Claxton S, Nadler M. Limitations of cyclosporine C2 monitoring in pediatric heart transplant recipients. Pediatr Transplant 2007;11:524-9.
147. Schubert S, bdul-Khaliq H, Lehmkuhl HB, et al. Advantages of C2 monitoring to avoid acute rejection in pediatric heart transplant recipients. J Heart Lung Transplant 2006;25:619-25.
148. Gajarski RJ, Crowley DC, Zamberlan MC, Lake KD. Lack of correlation between MMF dose and MPA level in pediatric and young adult cardiac transplant patients: does the MPA level matter? Am J Transplant 2004;4:1495-500.
149. Dipchand AI, Pietra B, McCrindle BW, Rosebrook-Bicknell HL, Boucek MM. Mycophenolic acid levels in pediatric heart transplant recipients receiving mycophenolate mofetil. J Heart Lung Transplant 2001;20:1035-43.
150. Halloran PF, Gourishankar S. Principles and overview of immunosuppression. In: Norman DJ, Laurel NJ, editors. Primer on transplantation. Mt Laurel, NJ: American Society of Transplantation; 2001. p. 87-98.
151. Scheinman RI, Cogswell PC, Lofquist AK, Baldwin AS Jr. Role of transcriptional activation of I kappa B alpha in mediation of immunosuppression by glucocorticoids. Science 1995;270:283-6.
152. Teuteberg JJ, Shullo M, Zomak R, et al. Aggressive steroid weaning after cardiac transplantation is possible without the additional risk of significant rejection. Clin Transplant 2008;22:730-7.
153. Taylor DO, Barr ML, Radovancevic B, et al. A randomized, multicenter comparison of tacrolimus and cyclosporine immunosuppressive regimens in cardiac transplantation: decreased hyperlipidemia and hypertension with tacrolimus. J Heart Lung Transplant 1999;18: 336-45.
154. Grimm M, Rinaldi M, Yonan NA, et al. Superior prevention of acute rejection by tacrolimus vs. cyclosporine in heart transplant recipients—a large European trial. Am J Transplant 2006;6:1387-97.
155. Mancini D, Pinney S, Burkhoff D, et al. Use of rapamycin slows progression of cardiac transplantation vasculopathy. Circulation 2003;108:48-53.
156. Keogh A, Richardson M, Ruygrok P, et al. Sirolimus in de novo heart transplant recipients reduces acute rejection and prevents coronary artery disease at 2 years: a randomized clinical trial. Circulation 2004;110:2694-700.
157. Eisen HJ, Tuzcu EM, Dorent R, et al. Everolimus for the prevention of allograft rejection and vasculopathy in cardiac-transplant recipients. N Engl J Med 2003;349:847-58.
158. Kobashigawa JA, Miller LW, Russell SD, et al. Tacrolimus with mycophenolate mofetil (MMF) or sirolimus vs. cyclosporine with MMF in cardiac transplant patients: 1-year report. Am J Transplant 2006; 6:1377-86.
159. Baran DA, Zucker MJ, Arroyo LH, et al. Randomized trial of tacrolimus monotherapy: tacrolimus in combination, tacrolimus alone compared (the TICTAC trial). J Heart Lung Transplant 2007;26:992-7.
160. Lehmkuhl H, Livi U, Arizon J, et al. Results of a 12-month, multicenter, randomized trial of everolimus with reduced-exposure cyclosporine versus mycophenolate mofetil and standard-exposure cyclosporine in de novo cardiac transplantation recipients. J Heart Lung Transplant 2008;27(2S):S65.
161. Raichlin E, Khalpey Z, Kremers W, et al. Replacement of calcineurin-inhibitors with sirolimus as primary immunosuppression in stable cardiac transplant recipients. Transplantation 2007;84:467-74.
162. Groetzner J, Meiser B, Landwehr P, et al. Mycophenolate mofetil and sirolimus as calcineurin inhibitor-free immunosuppression for late cardiac-transplant recipients with chronic renal failure. Transplantation 2004;77:568-74.
163. Kobashigawa J, Miller L, Renlund D, et al. A randomized active-controlled trial of mycophenolate mofetil in heart transplant recipients. Mycophenolate Mofetil Investigators. Transplantation 1998;66: 507-15.
164. Kobashigawa JA, Tobis JM, Mentzer RM, et al. Mycophenolate mofetil reduces intimal thickness by intravascular ultrasound after heart transplant: reanalysis of the multicenter trial. Am J Transplant 2006;6:993-7.
165. Kirk AD. Induction immunosuppression. Transplantation 2006;82: 593-602.
166. Bonnefoy-Berard N, Revillard JP. Mechanisms of immunosuppression induced by antithymocyte globulins and OKT3. J Heart Lung Transplant 1996;15:435-42.
167. Bourdage JS, Hamlin DM. Comparative polyclonal antithymocyte globulin and antilymphocyte/antilymphoblast globulin anti-CD antigen analysis by flow cytometry. Transplantation 1995;59:1194-200.
168. Rebellato LM, Gross U, Verbanac KM, Thomas JM. A comprehensive definition of the major antibody specificities in polyclonal rabbit antithymocyte globulin. Transplantation 1994;57:685-94.
169. Crespo-Leiro MG, onso-Pulpon L, Arizon JM, et al. Influence of induction therapy, immunosuppressive regimen and anti-viral prophylaxis on development of lymphomas after heart transplantation: data from the Spanish Post-Heart Transplant Tumour Registry. J Heart Lung Transplant 2007;26:1105-9.
170. Barr ML, Sanchez JA, Seche LA, et al. Anti-CD3 monoclonal antibody induction therapy. Immunological equivalency with triple-drug therapy in heart transplantation. Circulation 1990;82(5 suppl): IV291-4.
171. Swinnen LJ, Costanzo-Nordin MR, Fisher SG, et al. Increased incidence of lymphoproliferative disorder after immunosuppression with the monoclonal antibody OKT3 in cardiac-transplant recipients. N Engl J Med 1990;323:1723-8.
172. Teuteberg J, Shullo M, Zomak R, et al. Alemtuzumab induction facilitates corticosteroid-free maintenance immunosuppression inhuman cardiac transplantation. J Heart Lung Transplant 2008;27:S201-2.
173. Pham SM, Jimenez J, Bednar BM, et al. Campath-1H in clinical heart transplantation. J Heart Lung Transplant 2006;25:S228.
174. Das B, Shoemaker L, Recto M, Austin E, Dowling R. Alemtuzumab (Campath-1H) induction in a pediatric heart transplant: successful outcome and rationale for its use. J Heart Lung Transplant 2008;27: 242-4.
175. Zuckermann AO, Grimm M, Czerny M, et al. Improved long-term results with thymoglobuline induction therapy after cardiac transplantation: a comparison of two different rabbit-antithymocyte globulines. Transplantation 2000;69:1890-8.
176. Macdonald PS, Mundy J, Keogh AM, Chang VP, Spratt PM. A prospective randomized study of prophylactic OKT3 versus equine antithymocyte globulin after heart transplantation—increased morbidity with OKT3. Transplantation 1993;55:110-6.
177. Goland S, Czer LS, Coleman B, et al. Induction therapy with thymoglobulin after heart transplantation: impact of therapy duration on lymphocyte depletion and recovery, rejection, and cytomegalovirus infection rates. J Heart Lung Transplant 2008;27:1115-21.
178. Delgado DH, Miriuka SG, Cusimano RJ, et al. Use of basiliximab and cyclosporine in heart transplant patients with pre-operative renal dysfunction. J Heart Lung Transplant 2005;24:166-9.

179. Cantarovich M, Giannetti N, Barkun J, Cecere R. Antithymocyte globulin induction allows a prolonged delay in the initiation of cyclosporine in heart transplant patients with postoperative renal dysfunction. Transplantation 2004;78:779-81.
180. Beniaminovitz A, Itescu S, Lietz K, et al. Prevention of rejection in cardiac transplantation by blockade of the interleukin-2 receptor with a monoclonal antibody. N Engl J Med 2000;342:613-9.
181. Hershberger RE, Starling RC, Eisen HJ, et al. Daclizumab to prevent rejection after cardiac transplantation. N Engl J Med 2005;352:2705-13.
182. Mehra MR, Zucker MJ, Wagoner L, et al. A multicenter, prospective, randomized, double-blind trial of basiliximab in heart transplantation. J Heart Lung Transplant 2005;24:1297-304.
183. Chin C, Pittson S, Luikart H, et al. Induction therapy for pediatric and adult heart transplantation: comparison between OKT3 and daclizumab. Transplantation 2005;80:477-81.
184. Segovia J, Rodriguez-Lambert JL, Crespo-Leiro MG, et al. A randomized multicenter comparison of basiliximab and muromonab (OKT3) in heart transplantation: SIMCOR study. Transplantation 2006;81:1542-8.
185. Carlsen J, Johansen M, Boesgaard S, et al. Induction therapy after cardiac transplantation: a comparison of anti-thymocyte globulin and daclizumab in the prevention of acute rejection. J Heart Lung Transplant 2005;24:296-302.
186. Carrier M, Leblanc MH, Perrault LP, et al. Basiliximab and rabbit anti-thymocyte globulin for prophylaxis of acute rejection after heart transplantation: a non-inferiority trial. J Heart Lung Transplant 2007; 26:258-63.
187. Mattei MF, Redonnet M, Gandjbakhch I, et al. Lower risk of infectious deaths in cardiac transplant patients receiving basiliximab versus anti-thymocyte globulin as induction therapy. J Heart Lung Transplant 2007;26:693-9.
188. Meiser B, Reichart B, Adamidis I, Uberfuhr P, Kaczmarek I. First experience with de novo calcineurin-inhibitor-free immunosuppression following cardiac transplantation. Am J Transplant 2005;5:827-31.
189. Gonzalez-Vilchez F, de Prada JA, Exposito V, et al. Avoidance of calcineurin inhibitors with use of proliferation signal inhibitors in de novo heart transplantation with renal failure. J Heart Lung Transplant 2008;27:1135-41.
190. Lebeck LK, Chang L, Lopez-McCormack C, Chinnock R, Boucek M. Polyclonal antithymocyte serum: immune prophylaxis and rejection therapy in pediatric heart transplantation patients. J Heart Lung Transplant 1993;12:S286-92.
191. Parisi F, Danesi H, Squitieri C, Di Chiara L, Ravà L, Di Donato RM. Thymoglobuline use in pediatric heart transplantation. J Heart Lung Transplant 2003;22:591-3.
192. Pollock-Barziv SM, lain-Rooney T, Manlhiot C, et al. Continuous infusion of thymoglobulin for induction therapy in pediatric heart transplant recipients; experience and outcomes with a novel strategy for administration. Pediatr Transplant 2009;13:585-9.
193. Boucek RJ Jr, Naftel D, Boucek MM, et al. Induction immunotherapy in pediatric heart transplant recipients: a multicenter study. J Heart Lung Transplant 1999;18:460-9.
194. Kobashigawa JA, Katznelson S, Laks H, et al. Effect of pravastatin on outcomes after cardiac transplantation. N Engl J Med 1995;333: 621-7.
195. Wenke K, Meiser B, Thiery J, et al. Simvastatin reduces graft vessel disease and mortality after heart transplantation: a four-year randomized trial. Circulation 1997;96:1398-402.
196. Weitz-Schmidt G, Welzenbach K, Brinkmann V, et al. Statins selectively inhibit leukocyte function antigen-1 by binding to a novel regulatory integrin site. Nat Med 2001;7:687-92.
197. Weis M, Pehlivanli S, Meiser BM, von SW. Simvastatin treatment is associated with improvement in coronary endothelial function and decreased cytokine activation in patients after heart transplantation. J Am Coll Cardiol 2001;38:814-8.
198. Kobashigawa JA, Moriguchi JD, Laks H, et al. Ten-year follow-up of a randomized trial of pravastatin in heart transplant patients. J Heart Lung Transplant 2005;24:1736-40.
199. Wenke K, Meiser B, Thiery J, et al. Simvastatin initiated early after heart transplantation: 8-year prospective experience. Circulation 2003;107:93-7.
200. Mehra MR, Uber PA, Vivekananthan K, et al. Comparative beneficial effects of simvastatin and pravastatin on cardiac allograft rejection and survival. J Am Coll Cardiol 2002;40:1609-14.
201. Magnani G, Carinci V, Magelli C, et al. Role of statins in the management of dyslipidemia after cardiac transplant: randomized controlled trial comparing the efficacy and the safety of atorvastatin with pravastatin. J Heart Lung Transplant 2000;19:710-5.
202. Samman A, Imai C, Straatman L, et al. Safety and efficacy of rosuvastatin therapy for the prevention of hyperlipidemia in adult cardiac transplant recipients. J Heart Lung Transplant 2005;24:1008-13.
203. Penson MG, Fricker FJ, Thompson JR, et al. Safety and efficacy of pravastatin therapy for the prevention of hyperlipidemia in pediatric and adolescent cardiac transplant recipients. J Heart Lung Transplant 2001;20:611-8.
204. Chin C, Gamberg P, Miller J, Luikart H, Bernstein D. Efficacy and safety of atorvastatin after pediatric heart transplantation. J Heart Lung Transplant 2002;21:1213-7.
205. Hedman M, Neuvonen PJ, Neuvonen M, Holmberg C, Antikainen M. Pharmacokinetics and pharmacodynamics of pravastatin in pediatric and adolescent cardiac transplant recipients on a regimen of triple immunosuppression. Clin Pharmacol Ther 2004;75:101-9.
206. Mahle WT, Vincent RN, Berg AM, Kanter KR. Pravastatin therapy is associated with reduction in coronary allograft vasculopathy in pediatric heart transplantation. J Heart Lung Transplant 2005;24:63-6.
207. Chin C, Lukito SS, Shek J, Bernstein D, Perry SB. Prevention of pediatric graft coronary artery disease: atorvastatin. Pediatr Transplant 2008;12:442-6.
208. Zuppan CW, Wells LM, Kerstetter JC, et al. Cause of death in pediatric and infant heart transplant recipients: review of a 20-year, single-institution cohort. J Heart Lung Transplant 2009;28:579-84.
209. Reichart B, Meiser B, Vigano M, et al. European multicenter tacrolimus heart pilot study: three year follow-up. J Heart Lung Transplant 2001;20:249-50.
210. Bilchick KC, Henrikson CA, Skojec D, Kasper EK, Blumenthal RS. Treatment of hyperlipidemia in cardiac transplant recipients. Am Heart J 2004;148:200-10.
211. Heublein B, Wahlers T, Haverich A. Pulsed steroids for treatment of cardiac rejection after transplantation. What dosage is necessary? Circulation 1989;80:III97-9.
212. Lonquist JL, Radovancevic B, Vega JD, et al. Reevaluation of steroid tapering after steroid pulse therapy for heart rejection. J Heart Lung Transplant 1992;11:913-9.
213. Haverty TP, Sanders M, Sheahan M. OKT3 treatment of cardiac allograft rejection. J Heart Lung Transplant 1993;12:591-8.
214. Woodside KJ, Lick SD. Alemtuzumab (Campath 1H) as successful salvage therapy for recurrent steroid-resistant heart transplant rejection. J Heart Lung Transplant 2007;26:750-2.
215. Onsager DR, Canver CC, Jahania MS, et al. Efficacy of tacrolimus in the treatment of refractory rejection in heart and lung transplant recipients. J Heart Lung Transplant 1999;18:448-55.
216. Chan MC, Kwok BW, Shiba N, et al. Conversion of cyclosporine to tacrolimus for refractory or persistent myocardial rejection. Transplant Proc 2002;34:1850-2.
217. Yamani MH, Starling RC, Pelegrin D, et al. Efficacy of tacrolimus in patients with steroid-resistant cardiac allograft cellular rejection. J Heart Lung Transplant 2000;19:337-42.
218. Costanzo-Nordin MR, McManus BM, Wilson JE, et al. Efficacy of photopheresis in the rescue therapy of acute cellular rejection in human heart allografts: a preliminary clinical and immunopathologic report. Transplant Proc 1993;25:881-3.
219. Keogh AM, Arnold RH, Macdonald PS, et al. A randomized trial of tacrolimus (FK506) versus total lymphoid irradiation for the control of repetitive rejection after cardiac transplantation. J Heart Lung Transplant 2001;20:1331-4.

220. Atluri P, Hiesinger W, Gorman RC, et al. Cardiac retransplantation is an efficacious therapy for primary cardiac allograft failure. J Cardiothorac Surg 2008;3:26.
221. Grauhan O, Knosalla C, Ewert R, et al. Plasmapheresis and cyclophosphamide in the treatment of humoral rejection after heart transplantation. J Heart Lung Transplant 2001;20:316-21.
222. Kaczmarek I, Deutsch MA, Sadoni S, et al. Successful management of antibody-mediated cardiac allograft rejection with combined immunoadsorption and anti-CD20 monoclonal antibody treatment: case report and literature review. J Heart Lung Transplant 2007;26:511-5.
223. Garrett HE Jr, Duvall-Seaman D, Helsley B, Groshart K. Treatment of vascular rejection with rituximab in cardiac transplantation. J Heart Lung Transplant 2005;24:1337-42.
224. Rose ML, Smith J, Dureau G, Keogh A, Kobashigowa J. Mycophenolate mofetil decreases antibody production after cardiac transplantation. J Heart Lung Transplant 2002;21:282-5.
225. Itescu S, Burke E, Lietz K, et al. Intravenous pulse administration of cyclophosphamide is an effective and safe treatment for sensitized cardiac allograft recipients. Circulation 2002;105:1214-9.
226. Leech SH, Lopez-Cepero M, LeFor WM, et al. Management of the sensitized cardiac recipient: the use of plasmapheresis and intravenous immunoglobulin. Clin Transplant 2006;20:476-84.
227. Kfoury AG, Hammond ME, Snow GL, et al. Early screening for antibody-mediated rejection in heart transplant recipients. J Heart Lung Transplant 2007;26:1264-9.
228. Michaels PJ, Espejo ML, Kobashigawa J, et al. Humoral rejection in cardiac transplantation: risk factors, hemodynamic consequences and relationship to transplant coronary artery disease. J Heart Lung Transplant 2003;22:58-69.
229. Miller LW, Wesp A, Jennison SH, et al. Vascular rejection in heart transplant recipients. J Heart Lung Transplant 1993;12:S147-52.
230. Brunner-La Rocca HP, Schneider J, Kunzli A, Turina M, Kiowski W. Cardiac allograft rejection late after transplantation is a risk factor for graft coronary artery disease. Transplantation 1998;65:538-43.
231. Klingenberg R, Koch A, Schnabel PA, et al. Allograft rejection of ISHLT grade >/=3A occurring late after heart transplantation—a distinct entity? J Heart Lung Transplant 2003;22:1005-13.
232. Esmore DS, Spratt PM, Keogh AM, Chang VP. Cyclosporine and azathioprine immunosuppression without maintenance steroids: a prospective randomized trial. J Heart Transplant 1989;8:194-9.
233. Miller LW, Wolford T, McBride LR, Peigh P, Pennington DG. Successful withdrawal of corticosteroids in heart transplantation. J Heart Lung Transplant 1992;11:431-4.
234. Yamani MH, Taylor DO, Czerr J, et al. Thymoglobulin induction and steroid avoidance in cardiac transplantation: results of a prospective, randomized, controlled study. Clin Transplant 2008;22:76-81.
235. Angermann CE, Stork S, Costard-Jackle A, et al. Reduction of cyclosporine after introduction of mycophenolate mofetil improves chronic renal dysfunction in heart transplant recipients—the IMPROVED multi-centre study. Eur Heart J 2004;25:1626-34.
236. Rice JE, Shipp AT, Carlin JB, Vidmar SI, Weintraub RG. Late reduction in cyclosporine dosage does not improve renal function in pediatric heart transplant recipients. J Heart Lung Transplant 2002;21:1109-12.
237. Trosch F, Rothenburger M, Schneider M, et al. First experience with rapamycin-based immunosuppression to improve kidney function after heart transplantation. Thorac Cardiovasc Surg 2004;52:163-8.
238. Hamour IM, Lyster HS, Burke MM, Rose ML, Banner NR. Mycophenolate mofetil may allow cyclosporine and steroid sparing in de novo heart transplant patients. Transplantation 2007;83:570-6.
239. Gustafsson F, Ross HJ, Delgado MS, Bernabeo G, Delgado DH. Sirolimus-based immunosuppression after cardiac transplantation: predictors of recovery from calcineurin inhibitor-induced renal dysfunction. J Heart Lung Transplant 2007;26:998-1003.
240. Raichlin E, Bae JH, Khalpey Z, et al. Conversion to sirolimus as primary immunosuppression attenuates the progression of allograft vasculopathy after cardiac transplantation. Circulation 2007;116:2726-33.
241. Leonard H, Hornung T, Parry G, Dark JH. Pediatric cardiac transplant: results using a steroid-free maintenance regimen. Pediatr Transplant 2003;7:59-63.
242. Schachter AD, Meyers KE, Spaneas LD, et al. Short sirolimus half-life in pediatric renal transplant recipients on a calcineurin inhibitor-free protocol. Pediatr Transplant 2004;8:171-7.
243. van de Beek D, Kremers W, Daly RC, et al. Effect of neurologic complications on outcome after heart transplant. Arch Neurol 2008;65:226-31.
244. Zierer A, Melby SJ, Voeller RK, et al. Significance of neurologic complications in the modern era of cardiac transplantation. Ann Thorac Surg 2007;83:1684-90.
245. Mayer TO, Biller J, O'Donnell J, Meschia JF, Sokol DK. Contrasting the neurologic complications of cardiac transplantation in adults and children. J Child Neurol 2002;17:195-9.
246. Mateen FJ, van de BD, Kremers WK, et al. Neuromuscular diseases after cardiac transplantation. J Heart Lung Transplant 2009;28:226-30.
247. Kapadia SR, Nissen SE, Ziada KM, et al. Development of transplantation vasculopathy and progression of donor-transmitted atherosclerosis: comparison by serial intravascular ultrasound imaging. Circulation 1998;98:2672-8.
248. St Goar FG, Pinto FJ, Alderman EL, et al. Intracoronary ultrasound in cardiac transplant recipients. In vivo evidence of "angiographically silent" intimal thickening. Circulation 1992;85:979-87.
249. Kobashigawa JA, Tobis JM, Starling RC, et al. Multicenter intravascular ultrasound validation study among heart transplant recipients: outcomes after five years. J Am Coll Cardiol 2005;45:1532-7.
250. Nicolas RT, Kort HW, Balzer DT, et al. Surveillance for transplant coronary artery disease in infant, child and adolescent heart transplant recipients: an intravascular ultrasound study. J Heart Lung Transplant 2006;25:921-7.
251. Kuhn MA, Jutzy KR, Deming DD, et al. The medium-term findings in coronary arteries by intravascular ultrasound in infants and children after heart transplantation. J Am Coll Cardiol 2000;36:250-4.
252. Farzaneh-Far A. Electron-beam computed tomography in the assessment of coronary artery disease after heart transplantation. Circulation 2001;103:E60.
253. Pichler P, Loewe C, Roedler S, et al. Detection of high-grade stenoses with multislice computed tomography in heart transplant patients. J Heart Lung Transplant 2008;27:310-6.
254. Dipchand AI, Bharat W, Manlhiot C, et al. A prospective study of dobutamine stress echocardiography for the assessment of cardiac allograft vasculopathy in pediatric heart transplant recipients. Pediatr Transplant 2008;12:570-6.
255. Hacker M, Hoyer HX, Uebleis C, et al. Quantitative assessment of cardiac allograft vasculopathy by real-time myocardial contrast echocardiography: a comparison with conventional echocardiographic analyses and [Tc99m]-sestamibi SPECT. Eur J Echocardiogr 2008;9:494-500.
256. Eroglu E, D'hooge J, Sutherland GR, et al. Quantitative dobutamine stress echocardiography for the early detection of cardiac allograft vasculopathy in heart transplant recipients. Heart 2008;94:e3.
257. Mehra MR. Contemporary concepts in prevention and treatment of cardiac allograft vasculopathy. Am J Transplant 2006;6:1248-56.
258. Botha P, Peaston R, White K, et al. Smoking after cardiac transplantation. Am J Transplant 2008;8:866-71.
259. McDonald K, Rector TS, Braulin EA, Kubo SH, Olivari MT. Association of coronary artery disease in cardiac transplant recipients with cytomegalovirus infection. Am J Cardiol 1989;64:359-62.
260. Simmonds J, Fenton M, Dewar C, et al. Endothelial dysfunction and cytomegalovirus replication in pediatric heart transplantation. Circulation 2008;117:2657-61.
261. Hussain T, Burch M, Fenton MJ, et al. Positive pretransplantation cytomegalovirus serology is a risk factor for cardiac allograft vasculopathy in children. Circulation 2007;115:1798-1805.
262. Kato T, Chan MC, Gao SZ, et al. Glucose intolerance, as reflected by hemoglobin A1c level, is associated with the incidence and severity of transplant coronary artery disease. J Am Coll Cardiol 2004;43:1034-41.

263. Schroeder JS, Gao SZ, Alderman EL, et al. A preliminary study of diltiazem in the prevention of coronary artery disease in heart-transplant recipients. N Engl J Med 1993;328:164-70.
264. Erinc K, Yamani MH, Starling RC, et al. The effect of combined Angiotensin-converting enzyme inhibition and calcium antagonism on allograft coronary vasculopathy validated by intravascular ultrasound. J Heart Lung Transplant 2005;24:1033-8.
265. Halle AA, III, DiSciascio G, Massin EK, et al. Coronary angioplasty, atherectomy and bypass surgery in cardiac transplant recipients. J Am Coll Cardiol 1995;26:120-8.
266. Aqel RA, Wells BJ, Hage FG, et al. Re-stenosis after drug-eluting stents in cardiac allograft vasculopathy. J Heart Lung Transplant 2008;27:610-5.
267. Radovancevic B, McGiffin DC, Kobashigawa JA, et al. Retransplantation in 7,290 primary transplant patients: a 10-year multi-institutional study. J Heart Lung Transplant 2003;22:862-8.
268. Crespo-Leiro MG, onso-Pulpon L, Vazquez de Prada JA, et al. Malignancy after heart transplantation: incidence, prognosis and risk factors. Am J Transplant 2008;8:1031-9.
269. Webber SA, Naftel DC, Fricker FJ, et al. Lymphoproliferative disorders after paediatric heart transplantation: a multi-institutional study. Lancet 2006;367:233-9.
270. O'Neill JO, Edwards LB, Taylor DO. Mycophenolate mofetil and risk of developing malignancy after orthotopic heart transplantation: analysis of the transplant registry of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2006;25:1186-91.
271. Valantine H. Is there a role for proliferation signal/mTOR inhibitors in the prevention and treatment of de novo malignancies after heart transplantation? Lessons learned from renal transplantation and oncology. J Heart Lung Transplant 2007;26:557-64.
272. Senzolo M, Ferronato C, Burra P. Neurologic complications after solid organ transplantation. Transpl Int 2009;22:269-78.
273. Alonso EM. Long-term renal function in pediatric liver and heart recipients. Pediatr Transplant 2004;8:381-5.
274. Lee CK, Christensen LL, Magee JC, et al. Pre-transplant risk factors for chronic renal dysfunction after pediatric heart transplantation: a 10-year national cohort study. J Heart Lung Transplant 2007;26:458-65.
275. Wilkinson AH, Cohen DJ. Renal failure in the recipients of nonrenal solid organ transplants. J Am Soc Nephrol 1999;10:1136-44.
276. Ojo AO. Renal disease in recipients of nonrenal solid organ transplantation. Semin Nephrol 2007;27:498-507.
277. Bloom RD, Doyle AM. Kidney disease after heart and lung transplantation. Am J Transplant 2006;6:671-9.
278. Myers BD, Newton L. Cyclosporine-induced chronic nephropathy: an obliterative microvascular renal injury. J Am Soc Nephrol 1991;2(2 suppl 1):S45-52.
279. Kopp JB, Klotman PE. Cellular and molecular mechanisms of cyclosporin nephrotoxicity. J Am Soc Nephrol 1990;1:162-79.
280. Schmid H, Burg M, Kretzler M, et al. BK virus associated nephropathy in native kidneys of a heart allograft recipient. Am J Transplant 2005;5:1562-8.
281. Randhawa P, Brennan DC. BK virus infection in transplant recipients: an overview and update. Am J Transplant 2006;6:2000-5.
282. Gleissner CA, Murat A, Schafer S, et al. Reduced hemoglobin after heart transplantation is no independent risk factor for survival but is associated closely with impaired renal function. Transplantation 2004;77:710-7.
283. Marchetti P. New-onset diabetes after transplantation. J Heart Lung Transplant 2004;23(5 suppl):S194-201.
284. Bloom RD, Crutchlow MF. Transplant-associated hyperglycemia. Transplant Rev (Orlando) 2008;22:39-51.
285. Hathout EH, Chinnock RE, Johnston JK, et al. Pediatric post-transplant diabetes: data from a large cohort of pediatric heart-transplant recipients. Am J Transplant 2003;3:994-8.
286. Pham PT, Pham PC, Lipshutz GS, Wilkinson AH. New onset diabetes mellitus after solid organ transplantation. Endocrinol Metab Clin North Am 2007;36:873-90.
287. Davidson J, Wilkinson A, Dantal J, et al. New-onset diabetes after transplantation: 2003 International consensus guidelines. Proceedings of an international expert panel meeting. Barcelona, Spain, 19 February 2003. Transplantation 2003;75(10 suppl):SS3-24.
288. Wilkinson A, Davidson J, Dotta F, et al. Guidelines for the treatment and management of new-onset diabetes after transplantation. Clin Transplant 2005;19:291-8.
289. Kuppahally S, Al-Khaldi A, Weisshaar D, et al. Wound healing complications with de novo sirolimus versus mycophenolate mofetil-based regimen in cardiac transplant recipients. Am J Transplant 2006;6:986-92.
290. Diaz B, Gonzalez VF, Almenar L, et al. Gastrointestinal complications in heart transplant patients: MITOS study. Transplant Proc 2007;39:2397-400.
291. Kobashigawa JA, Renlund DG, Gerosa G, et al. Similar efficacy and safety of enteric-coated mycophenolate sodium (EC-MPS, myfortic) compared with mycophenolate mofetil (MMF) in de novo heart transplant recipients: results of a 12-month, single-blind, randomized, parallel-group, multicenter study. J Heart Lung Transplant 2006;25:935-41.
292. Galiwango PJ, Delgado DH, Yan R, et al. Mycophenolate mofetil dose reduction for gastrointestinal intolerance is associated with increased rates of rejection in heart transplant patients. J Heart Lung Transplant 2008;27:72-7.
293. Felkel TO, Smith AL, Reichenspurner HC, et al. Survival and incidence of acute rejection in heart transplant recipients undergoing successful withdrawal from steroid therapy. J Heart Lung Transplant 2002;21:530-9.
294. Saeed SA, Integlia MJ, Pleskow RG, et al. Tacrolimus-associated eosinophilic gastroenterocolitis in pediatric liver transplant recipients: role of potential food allergies in pathogenesis. Pediatr Transplant 2006;10:730-5.
295. Woo SB, Treister N. Ciclosporin-induced fibrovascular polyps vs. bacillary angiomatosis. Br J Dermatol 2008;158:652-3.
296. De Iudicibus S, Castronovo G, Gigante A, et al. Role of MDR1 gene polymorphisms in gingival overgrowth induced by cyclosporine in transplant patients. J Periodontal Res 2008;43:665-72.
297. Ozdemir O, rrey-Mensah A, Sorensen RU. Development of multiple food allergies in children taking tacrolimus after heart and liver transplantation. Pediatr Transplant 2006;10:380-3.
298. Fuchs U, Zittermann A, Berthold HK, et al. Immunosuppressive therapy with everolimus can be associated with potentially life-threatening lingual angioedema. Transplantation 2005;79:981-3.
299. Exposito V, de Prada JA, Gomez-Roman JJ, et al. Everolimus-related pulmonary toxicity in heart transplant recipients. J Heart Lung Transplant 2008;27:797-800.
300. Lindenfeld JA, Simon SF, Zamora MR, et al. BOOP is common in cardiac transplant recipients switched from a calcineurin inhibitor to sirolimus. Am J Transplant 2005;5:1392-6.
301. Lubbe J, Sorg O, Male PJ, Saurat JH, Masouye I. Sirolimus-induced inflammatory papules with acquired reactive perforating collagenosis. Dermatology 2008;216:239-42.
302. Deutsch MA, Kaczmarek I, Huber S, et al. Sirolimus-associated infertility: case report and literature review of possible mechanisms. Am J Transplant 2007;7:2414-21.
303. Raza S, Ullah K, Ahmed P, et al. Cyclosporine induced neurotoxicity in a stem cell transplant recipient. J Pak Med Assoc 2007;57:611-3.
304. Morelli N, Mancuso M, Caffori G, Gori S, Murri L. Reversible brachial diplegia in a case treated with cyclosporine. Neurology 2007;69:220.
305. Sevmis S, Karakayali H, Emiroglu R, Akkoc H, Haberal M. Tacrolimus-related seizure in the early postoperative period after liver transplantation. Transplant Proc 2007;39:1211-3.
306. Kaczmarek I, Schmauss D, Sodian R, et al. Late-onset tacrolimus-associated cerebellar atrophia in a heart transplant recipient. J Heart Lung Transplant 2007;26:89-92.
307. Norman K, Bonatti H, Dickson RC, randa-Michel J. Sudden hearing loss associated with tacrolimus in a liver transplant recipient. Transpl Int 2006;19:601-3.

308. Frantzeskaki F, Paramythiotou E, Papathanasiou M, et al. Posterior reversible encephalopathy syndrome in an intensive care unit patient receiving tacrolimus. Acta Anaesthesiol Scand 2008;52:1177.
309. De Weerdt A, Claeys KG, De JP, et al. Tacrolimus-related polyneuropathy: case report and review of the literature. Clin Neurol Neurosurg 2008;110:291-4.
310. Miyagi S, Sekiguchi S, Kawagishi N, et al. Parkinsonism during cyclosporine treatment in liver transplantation: an unusual case report. Transplant Proc 2008;40:2823-2824.
311. Up to Date Online. http://www.uptodateonline.com. 2010.
312. Lipshutz GS, Pham PC, Ghobrial MR, et al. Thrombotic microangiopathy following pancreas after kidney transplants. Clin Transplant 2008;22:236-41.
313. Tricot L, Lebbe C, Pillebout E, et al. Tacrolimus-induced alopecia in female kidney-pancreas transplant recipients. Transplantation 2005; 80:1546-9.
314. Kim PT, Davis JE, Erb SR, Yoshida EM, Steinbrecher UP. Colonic malakoplakia in a liver transplant recipient. Can J Gastroenterol 2007;21:753-5.
315. Taniai N, Akimaru K, Ishikawa Y, et al. Hepatotoxicity caused by both tacrolimus and cyclosporine after living donor liver transplantation. J Nippon Med Sch 2008;75:187-91.
316. Shah S, Budev M, Blazey H, Fairbanks K, Mehta A. Hepatic venoocclusive disease due to tacrolimus in a single-lung transplant patient. Eur Respir J 2006;27:1066-8.
317. Blanchard SS, Gerrek M, Czinn S, et al. Food protein sensitivity with partial villous atrophy after pediatric liver transplantation with tacrolimus immunosuppression. Pediatr Transplant 2006;10:529-32.
318. McCalmont V, Bennett K. Progressive multifocal leukoencephalopathy: a case study. Prog Transplant 2007;17:157-60.
319. Papali A, Giannetti N, Cantarovich M. Unilateral upper extremity edema associated with sirolimus in a heart transplant patient. Transplantation 2007;83:240.
320. van Onna M, Geerts A, Van VH, et al. One-sided limb lymphedema in a liver transplant recipient receiving sirolimus. Acta Gastroenterol Belg 2007;70:357-9.
321. Garcia-Luque A, Cordero E, Torello J, et al. Sirolimus-associated pneumonitis in heart transplant recipients. Ann Pharmacother 2008; 42:1143-5.
322. Perez MJ, Martin RO, Garcia DM, et al. Interstitial pneumonitis associated with sirolimus in liver transplantation: a case report. Transplant Proc 2007;39:3498-9.
323. Tracey C, Hawley C, Griffin AD, Strutton G, Lynch S. Generalized, pruritic, ulcerating maculopapular rash necessitating cessation of sirolimus in a liver transplantation patient. Liver Transpl 2005;11: 987-9.
324. Zakliczynski M, Nozynski J, Kocher A, et al. Surgical wound-healing complications in heart transplant recipients treated with rapamycin. Wound Repair Regen 2007;15:316-21.
325. Neff GW, Ruiz P, Madariaga JR, et al. Sirolimus-associated hepatotoxicity in liver transplantation. Ann Pharmacother 2004;38:1593-6.
326. Smith AD, Bai D, Marroquin CE, et al. Gastrointestinal hemorrhage due to complicated gastroduodenal ulcer disease in liver transplant patients taking sirolimus. Clin Transplant 2005;19:250-4.
327. Schacherer D, Zeitoun M, Buttner R, et al. Sirolimus-induced drug fever and ciclosporin-induced leukencephalopathia with seizures in one liver transplant recipient. World J Gastroenterol 2007;13:6090-3.
328. Shipkova M, Armstrong VW, Oellerich M, Wieland E. Mycophenolate mofetil in organ transplantation: focus on metabolism, safety and tolerability. Expert Opin Drug Metab Toxicol 2005;1:505-26.
329. Eisen HJ, Kobashigawa J, Keogh A, et al. Three-year results of a randomized, double-blind, controlled trial of mycophenolate mofetil versus azathioprine in cardiac transplant recipients. J Heart Lung Transplant 2005;24:517-25.
330. Kapetanakis EI, Antonopoulos AS, Antoniou TA, et al. Effect of long-term calcitonin administration on steroid-induced osteoporosis after cardiac transplantation. J Heart Lung Transplant 2005;24:526-32.
331. Yong G, Hayes H, O'Driscoll G. Strategy of aggressive steroid weaning and routine alendronate therapy to reduce bone loss after cardiac transplantation. Transplant Proc 2007;39:3340-3.
332. Shane E, Rivas M, McMahon DJ, et al. Bone loss and turnover after cardiac transplantation. J Clin Endocrinol Metab 1997;82:1497-506.
333. Cremer J, Struber M, Wagenbreth I, et al. Progression of steroid-associated osteoporosis after heart transplantation. Ann Thorac Surg 1999;67:130-3.
334. Lindenfeld J, Page RL, Zolty R, et al. Drug therapy in the heart transplant recipient: part III: common medical problems. Circulation 2005;111:113-7.
335. Sanchez-Lazaro IJ, Martinez-Dolz L, menar-Bonet L, et al. Predictor factors for the development of arterial hypertension following heart transplantation. Clin Transplant 2008;22:760-4.
336. Klinge A, Allen J, Murray A, O'Sullivan J. Increased pulse wave velocity and blood pressure in children who have undergone cardiac transplantation. J Heart Lung Transplant 2009;28:21-5.
337. Walker AH, Locke TJ, Braidley PC, Al-Mohammed A. The importance of 24 hour ambulatory blood pressure monitoring after thoracic organ transplantation. J Heart Lung Transplant 2005;24:1770-3.
338. Roche SL, Kaufmann J, Dipchand AI, Kantor PF. Hypertension after pediatric heart transplantation is primarily associated with immunosuppressive regimen. J Heart Lung Transplant 2008;27:501-7.
339. Brozena SC, Johnson MR, Ventura H, et al. Effectiveness and safety of diltiazem or lisinopril in treatment of hypertension after heart transplantation. Results of a prospective, randomized multicenter trail. J Am Coll Cardiol 1996;27:1707-12.
340. Mathias HC, Ozalp F, Will MB, et al. A randomized, controlled trial of C0- Vs C2-guided therapeutic drug monitoring of cyclosporine in stable heart transplant patients. J Heart Lung Transplant 2005;24: 2137-43.
341. Canter CE, Moorhead S, Saffitz JE, Huddleston CB, Spray TL. Steroid withdrawal in the pediatric heart transplant recipient initially treated with triple immunosuppression. J Heart Lung Transplant 1994;13:74-9.
342. Lee AH, Mull RL, Keenan GF, et al. Osteoporosis and bone morbidity in cardiac transplant recipients. Am J Med 1994;96:35-41.
343. Pisani B, Mullen GM. Prevention of osteoporosis in cardiac transplant recipients. Curr Opin Cardiol 2002;17:160-4.
344. Guo CY, Johnson A, Locke TJ, Eastell R. Mechanisms of bone loss after cardiac transplantation. Bone 1998;22:267-71.
345. Shane E, Addesso V, Namerow PB, et al. Alendronate versus calcitriol for the prevention of bone loss after cardiac transplantation. N Engl J Med 2004;350:767-76.
346. Leidig-Bruckner G, Hosch S, Dodidou P, et al. Frequency and predictors of osteoporotic fractures after cardiac or liver transplantation: a follow-up study. Lancet 2001;357:342-7.
347. Braith RW, Magyari PM, Fulton MN, et al. Resistance exercise training and alendronate reverse glucocorticoid-induced osteoporosis in heart transplant recipients. J Heart Lung Transplant 2003;22:1082-90.
348. Braith RW, Magyari PM, Fulton MN, et al. Comparison of calcitonin versus calcitonin + resistance exercise as prophylaxis for osteoporosis in heart transplant recipients. Transplantation 2006;81:1191-5.
349. Van Cleemput J, Daenen W, Geusens P, et al. Prevention of bone loss in cardiac transplant recipients. A comparison of biphosphonates and vitamin D. Transplantation 1996;61:1495-9.
350. Cohen A, Addesso V, McMahon DJ, et al. Discontinuing antiresorptive therapy one year after cardiac transplantation: effect on bone density and bone turnover. Transplantation 2006;81:686-91.
351. Dodidou P, Bruckner T, Hosch S, et al. Better late than never? Experience with intravenous pamidronate treatment in patients with low bone mass or fractures following cardiac or liver transplantation. Osteoporos Int 2003;14:82-9.
352. Coscia LA, Constantinescu S, Moritz MJ, et al. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. Clin Transpl 2007;29-42.
353. Sibanda N, Briggs JD, Davison JM, Johnson RJ, Rudge CJ. Pregnancy after organ transplantation: a report from the UK Transplant pregnancy registry. Transplantation 2007;83:1301-7.

354. Transfer of drugs and other chemicals into human milk. Pediatrics 2001;108:776-89.
355. Estes CM, Westhoff C. Contraception for the transplant patient. Semin Perinatol 2007;31:372-7.
356. Sucato GS, Murray PJ. Gynecologic health care for the adolescent solid organ transplant recipient. Pediatr Transplant 2005;9:346-56.
357. McKay DB, Josephson MA, Armenti VT, et al. Reproduction and transplantation: report on the AST Consensus Conference on Reproductive Issues and Transplantation. Am J Transplant 2005;5:1592-9.
358. Schofield RS, Edwards DG, Schuler BT, et al. Vascular effects of sildenafil in hypertensive cardiac transplant recipients. Am J Hypertens 2003;16:874-7.
359. Marconi C, Marzorati M. Exercise after heart transplantation. Eur J Appl Physiol 2003;90:250-9.
360. Biring MS, Fournier M, Ross DJ, Lewis MI. Cellular adaptations of skeletal muscles to cyclosporine. J Appl Physiol 1998;84:1967-75.
361. Niset G, Hermans L, Depelchin P. Exercise and heart transplantation. A review. Sports Med 1991;12:359-79.
362. Keteyian S, Shepard R, Ehrman J, et al. Cardiovascular responses of heart transplant patients to exercise training. J Appl Physiol 1991;70:2627-31.
363. Kobashigawa JA, Leaf DA, Lee N, et al. A controlled trial of exercise rehabilitation after heart transplantation. N Engl J Med 1999;340:272-7.
364. Braith RW, Schofield RS, Hill JA, Casey DP, Pierce GL. Exercise training attenuates progressive decline in brachial artery reactivity in heart transplant recipients. J Heart Lung Transplant 2008;27:52-9.
365. Pierce GL, Schofield RS, Casey DP, et al. Effects of exercise training on forearm and calf vasodilation and proinflammatory markers in recent heart transplant recipients: a pilot study. Eur J Cardiovasc Prev Rehabil 2008;15:10-8.
366. Haykowsky M, Taylor D, Kim D, Tymchak W. Exercise training improves aerobic capacity and skeletal muscle function in heart transplant recipients. Am J Transplant 2009;9:734-9.
367. Braith RW, Welsch MA, Mills RM Jr, Keller JW, Pollock ML. Resistance exercise prevents glucocorticoid-induced myopathy in heart transplant recipients. Med Sci Sports Exerc 1998;30:483-9.
368. Patel JN, Kavey RE, Pophal SG, et al. Improved exercise performance in pediatric heart transplant recipients after home exercise training. Pediatr Transplant 2008;12:336-40.
369. Blasco LM, Parameshwar J, Vuylsteke A. Anaesthesia for noncardiac surgery in the heart transplant recipient. Curr Opin Anaesthesiol 2009;22:109-13.
370. Kavanagh T, Yacoub MH, Kennedy J, Austin PC. Return to work after heart transplantation: 12-year follow-up. J Heart Lung Transplant 1999;18:846-51.
371. Paris W, Woodbury A, Thompson S, et al. Social rehabilitation and return to work after cardiac transplantation—a multicenter survey. Transplantation 1992;53:433-8.
372. White-Williams C, Jalowiec A, Grady K. Who returns to work after heart transplantation? J Heart Lung Transplant 2005;24:2255-61.
373. Tjang YS, Tenderich G, Hornik L, Korfer R. Cardiac retransplantation in adults: an evidence-based systematic review. Thorac Cardiovasc Surg 2008;56:323-7.
374. Shuhaiber JH, Kim JB, Hur K, et al. Comparison of survival in primary and repeat heart transplantation from 1987 through 2004 in the United States. Ann Thorac Surg 2007;83:2135-41.
375. Chin C, Naftel D, Pahl E, et al. Cardiac re-transplantation in pediatrics: a multi-institutional study. J Heart Lung Transplant 2006;25:1420-4.
376. American Transplant Society. When to contact the transplant center: AST guidelines for non-transplant physicians caring for heart and/or lung transplant recipients. http://www.a-s-t.org/index2.cfm?Section=non_transp_phys. 2010.
377. Fusar-Poli P, Picchioni M, Martinelli V, et al. Anti-depressive therapies after heart transplantation. J Heart Lung Transplant 2006;25:785-93.
378. De Bleser L, Matteson M, Dobbels F, Russell C, De GS. Interventions to improve medication-adherence after transplantation: a systematic review. Transpl Int 2009;22:780-97.
379. Dew MA, DiMartini AF, De Vito DA, et al. Rates and risk factors for nonadherence to the medical regimen after adult solid organ transplantation. Transplantation 2007;83:858-73.
380. Havik OE, Sivertsen B, Relbo A, et al. Depressive symptoms and all-cause mortality after heart transplantation. Transplantation 2007;84:97-103.
381. Lawrence K, Stilley CS, Olshansky E, Bender A, Webber SA. Further exploration: maturity and adherence in adolescent and young adult heart transplant recipients. Prog Transplant 2008;18:50-4.
382. Szepietowski JC, Reich A, Nowicka D, Weglowska J, Szepietowski T. Sun protection in renal transplant recipients: urgent need for education. Dermatology 2005;211:93-7.
383. Wray J, Waters S, Radley-Smith R, Sensky T. Adherence in adolescents and young adults following heart or heart-lung transplantation. Pediatr Transplant 2006;10:694-700.
384. Dobbels F, Van Damme-Lombaert R, Vanhaecke J, De GS. Growing pains: non-adherence with the immunosuppressive regimen in adolescent transplant recipients. Pediatr Transplant 2005;9:381-90.
385. Keith DS, Cantarovich M, Paraskevas S, Tchervenkov J. Recipient age and risk of chronic allograft nephropathy in primary deceased donor kidney transplant. Transpl Int 2006;19:649-56.
386. Rosen DS, Blum RW, Britto M, Sawyer SM, Siegel DM. Transition to adult health care for adolescents and young adults with chronic conditions: position paper of the Society for Adolescent Medicine. J Adolesc Health 2003;33:309-11.
387. Williams MJ, Lee MY, DiSalvo TG, et al. Biopsy-induced flail tricuspid leaflet and tricuspid regurgitation following orthotopic cardiac transplantation. Am J Cardiol 1996;77:1339-44.
388. Nguyen V, Cantarovich M, Cecere R, Giannetti N. Tricuspid regurgitation after cardiac transplantation: how many biopsies are too many? J Heart Lung Transplant 2005;24(7 suppl):S227-31.
389. Wiklund L, Suurkula MB, Kjellstrom C, Berglin E. Chordal tissue in endomyocardial biopsies. Scand J Thorac Cardiovasc Surg 1994;28:13-8.
390. Mielniczuk L, Haddad H, Davies RA, Veinot JP. Tricuspid valve chordal tissue in endomyocardial biopsy specimens of patients with significant tricuspid regurgitation. J Heart Lung Transplant 2005;24:1586-90.
391. Levi DS, DeConde AS, Fishbein MC, et al. The yield of surveillance endomyocardial biopsies as a screen for cellular rejection in pediatric heart transplant patients. Pediatr Transplant 2004;8:22-8.
392. Billingham ME, Cary NR, Hammond ME, et al. A working formulation for the standardization of nomenclature in the diagnosis of heart and lung rejection: Heart Rejection Study Group. The International Society for Heart Transplantation. J Heart Transplant 1990;9:587-93.
393. Winters GL. The challenge of endomyocardial biopsy interpretation in assessing cardiac allograft rejection. Curr Opin Cardiol 1997;12:146-52.
394. Cai J, Terasaki PI. Humoral theory of transplantation: mechanism, prevention, and treatment. Hum Immunol 2005;66:334-42.
395. Delgado JF, Sanchez V, de la Calzada CS. Acute rejection after heart transplantation. Expert Opin Pharmacother 2006;7:1139-49.
396. Bierl C, Miller B, Prak EL, et al. Antibody-mediated rejection in heart transplant recipients: potential efficacy of B-cell depletion and antibody removal. Clin Transpl 2006;489-96.