



# The International Society for Heart and Lung Transplantation (ISHLT) guidelines for the care of heart transplant recipients

Angela Velleca, MHDS, RN,<sup>a,1</sup> Michael A Shullo, PharmD,<sup>b,1</sup>  
Kumud Dhital, BMCh, PhD,<sup>c</sup> Estela Azeka, MD,<sup>d</sup> Monica Colvin, MD,<sup>e</sup>  
Eugene DePasquale, MD,<sup>f</sup> Marta Farrero, MD, PhD,<sup>g</sup> Luis García-Guereta, MD,<sup>h</sup>  
Gina Jamero, NP,<sup>a</sup> Kiran Khush, MD,<sup>i</sup> Jacob Lavee, MD,<sup>j</sup>  
Stephanie Pouch, MD,<sup>k</sup> Jignesh Patel, MD, PhD,<sup>a</sup> CJ Michaud, PharmD,<sup>l</sup>  
Michael A Shullo, PharmD,<sup>b</sup> Stephan Schubert, MD,<sup>m</sup> Annalisa Angelini, MD,<sup>n</sup>  
Lilibeth Carlos, MPharm,<sup>o</sup> Sonia Mirabet, MD,<sup>p</sup> Jignesh Patel, MD, PhD,<sup>a</sup>  
Michael Pham, MD,<sup>q</sup> Simon Urschel, MD,<sup>r</sup> Kyung-Hee Kim, MD,<sup>s</sup>  
Shelly Miyamoto, MD,<sup>t</sup> Sharon Chih, MD,<sup>u</sup> Kevin Daly, MD,<sup>v</sup> Paolo Grossi, MD,<sup>w</sup>  
Douglas L Jennings, PharmD,<sup>x,y</sup> In-cheol Kim, MD,<sup>z</sup> Hoong Sern Lim, MD,<sup>aa</sup>

Endorsed by the Pediatric Heart Transplant Society.

Independent Expert Reviewers: David Baran, Tiffany Buda, Adam Cochrane, Maria Crespo Leiro, Anne Dipchand, Brian Feingold, Kathleen Grady, Edward Horn, Maryl Johnson, Donna Mancini, Sean Pinney, Heather Ross, Kari Wujcik, Andreas Zuckermann. *Abbreviations:* AAIR, atrium paced, atrium sensed inhibited rate modulation; ABOi, ABO incompatible; ACC, American College of Cardiology; ACEI, angiotensin converting enzyme inhibitor; ACR, acute cellular rejection; 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; ASD, atrial septal defect; ATG, anti-thymocyte globulin; AV, arteriovenous; AZA, azathioprine; BiV, biventricular; BMD, bone mass density; BNP, brain natriuretic peptide; BPAR, proven acute rejection; CAV, cardiac allograft vasculopathy; CBCR, center-based cardiac rehabilitation; CCB, calcium channel blocker; CCTA, Coronary computed tomography angiography; CEDIA, cloned enzyme donor immunoassay method; CHD, congenital heart disease; CI, cardiac index; CKD, chronic kidney disease; CO, cardiac output; CPB, cardiopulmonary bypass; c-PRA, calculated PRA; 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; GEP, Gene Expression Profiling-Allomap; GFR, glomerular filtration rate; HBCR, Home-based cardiac rehabilitation; Hgb, hemoglobin; HIT, heparin-induced thrombocytopenia; HIV, Human Immunodeficiency virus;

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; IH, Isohemagglutinin; INR, international normalized unit; IABP, intra-aortic balloon pump; ISHLT, International Society for Heart and Lung Transplantation; IUD, intrauterine device; IV, intravenous; IVUS, intravascular ultrasound; LV, left ventricle; LVAD, left ventricular assist device; 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; MFI, mean fluorescent intensity; MMF, mycophenolate mofetil; MPA, mycophenolic acid; mTOR, mammalian target of rapamycin; MVO2, 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; PCSK9, Proprotein convertase subtilisin-kexin type 9; PSI, proliferation signal inhibitor; PTLD, posttransplant lymphoproliferative disorder; PT, prothrombin time; PTT, partial thromboplastin time; PVR, pulmonary vascular resistance; RAP, right atrial pressure; PCC, prothrombin plasma concentrates; PFA-100, platelets function assay 100; PGF, primary graft failure; PRA, panel reactive antibodies; PRES, posterior reversible leukoencephalopathy; PCSK9, Proprotein convertase subtilisin-kexin type 9; 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; SPECT, single-photon emission computed tomography; SRL, sirolimus; STI, sexually transmitted infection; SVT, sustained ventricular tachycardia; TAC, tacrolimus; TEE, transesophageal echocardiogram; TMP/SMZ, trimethoprim/sulfamethoxazole; TPG, Trans-Pulmonary Gradient; TTE, transthoracic echocardiogram; TV, tricuspid valve; VAD, ventricular assist device; VER, ventricular evoked responses; VT, ventricular tachycardia

Reprint requests: Michael A Shullo PharmD, West Virginia University Hospitals, Morgantown WV.

E-mail address: [Michael.Shullo@wvumedicine.org](mailto:Michael.Shullo@wvumedicine.org)

Tara Miller, MS,<sup>bb</sup> Luciano Potena, MD,<sup>cc</sup> Angela Velleca, MHDS, RN,<sup>a</sup>  
 Howard Eisen, MD,<sup>dd</sup> Lavanya Bellumkonda, MD,<sup>ee</sup> Lara Danziger-Isakov, MD,<sup>ff</sup>  
 Fabienne Dobbels, PhD,<sup>gg</sup> Michelle Harkess, RN,<sup>o</sup> Daniel Kim, MD,<sup>hh</sup>  
 Haifa Lyster, FRPharmS,<sup>ii</sup> Yael Peled, MD,<sup>jj</sup> and Zdenka Reinhardt, MD<sup>kk</sup>

From the <sup>a</sup>Cedars-Sinai Smidt Heart Institute, Los Angeles, California; <sup>b</sup>West Virginia University Hospitals, Morgantown West Virginia; <sup>c</sup>Kauvery Hospital, Chennai, India; <sup>d</sup>Instituto do Coracao (InCor), Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, Brazil; <sup>e</sup>University of Michigan, Ann Arbor, Michigan; <sup>f</sup>University of Southern California, Los Angeles, California; <sup>g</sup>Unitat d'Insuficiencia Cardíaca i Trasplantament Barcelona, Barcelona, Spain; <sup>h</sup>Pediatric Cardiology Department Hospital Universitario La Paz, Madrid, Spain; <sup>i</sup>Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, California; <sup>j</sup>Sheba Medical Center and the Tel Aviv University Faculty of Medicine, Tel Aviv, Israel; <sup>k</sup>Emory University, Atlanta, Georgia; <sup>l</sup>Spectrum Health, Grand Rapids, Michigan; <sup>m</sup>Center for Congenital Heart Disease/Pediatric Cardiology Heart- and Diabetescenter NRW, University Clinic of Ruhr-University Bochum, Bad Oeynhausen, Germany; <sup>n</sup>Dept of Cardiac, Thoracic and Vascular Sciences and Public Health, University of Padua, Padua, Italy; <sup>o</sup>St. Vincent's Hospital, Sydney, Australia; <sup>p</sup>Cardiology Department, Hospital Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain; <sup>q</sup>California Pacific Medical Center, San Francisco, California; <sup>r</sup>University of Alberta/Stollery Edmonton, Edmonton, Alberta, Canada; <sup>s</sup>Incheon Sejong Hospital, Incheon, South Korea; <sup>t</sup>University of Colorado & Children's Hospital Colorado, Aurora, Colorado; <sup>u</sup>University of Ottawa Heart Institute, Ottawa, Canada; <sup>v</sup>Boston Children's Hospital & Harvard Medical School, Boston Massachusetts; <sup>w</sup>Department of Medicine and Surgery, University of Insubria, Varese, Italy; <sup>x</sup>Department of Pharmacy, New York-Presbyterian Hospital Columbia University Irving Medical Center, New York, New York; <sup>y</sup>Department of Pharmacy Practice, Arnold & Marie Schwartz College of Pharmacy, Long Island University, New York, New York; <sup>z</sup>Cardiovascular Center Keimyung University Dongsan Hospital, Keimyung University School of Medicine, Daegu, South Korea; <sup>aa</sup>University Hospitals Birmingham NHS Foundation Trust, Birmingham, England; <sup>bb</sup>Duke University, Durham, North Carolina; <sup>cc</sup>Unit for Heart Failure and Transplantation, IRCCS Azienda Ospedaliero-Universitaria di Bologna; <sup>dd</sup>Penn State University, State College, Pennsylvania; <sup>ee</sup>Yale University, New Haven, Connecticut; <sup>ff</sup>Cincinnati Children's Hospital, Cincinnati, Ohio; <sup>gg</sup>KU Leuven, Department of Public Health and Primary Care, Academic Center for Nursing and Midwifery, Leuven, Belgium; <sup>hh</sup>University of Alberta & Mazankowski Alberta Heart Institute, Edmonton Alberta, Canada; <sup>ii</sup>Royal Brompton & Harefield Hospitals, Harefield, England; <sup>jj</sup>Sheba Medical Center, Tel Aviv, Israel; and the <sup>kk</sup>Freeman Hospital, Newcastle upon Tyne, UK.

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The International Society for Heart and Lung Transplantation (ISHLT) Guidelines for the Care of Heart Transplant Recipients were originally published in 2010.<sup>635</sup> These guidelines provided the first comprehensive guideline for the care of Heart Transplant patients. A great deal has changed in the years after this initial unprecedented document. The ISHLT has made the commitment to convene experts in all areas of heart transplantation to develop a focused update to the original practice guidelines. Writers and Chairs were charged with reviewing the existing guidelines and where significant new literature exists, updating those original recommendations. Additionally, they were

charged to add specific new areas of focus that were undeveloped, undiscovered, or unsupported at the time of the original publication. After a vast effort involving 39 writers from 11 countries worldwide, the "ISHLT Guidelines for the Care of Heart Transplant Recipients" has now been completed and the Executive Summary of these guidelines is the subject of this article.

The document results from the work of 4 Task Force groups each co-chaired by a pediatric heart transplant clinician who had the specific mandate to highlight issues unique to the pediatric heart transplant population and to ensure their adequate representation.

<sup>1</sup>Co-first authors

- Task Force 1 addresses the perioperative care of heart transplant recipients, including:
  - Pre-Transplant Optimization
  - Surgical Issues Impacting Care in the Immediate Post-operative Period
  - Considerations in Patients Bridged with Mechanical Circulatory Support
  - Early Post-Operative Care of the Heart Transplant Recipient
  - Evaluation of Allosensitization, Approaches to Sensitized Heart Transplant Recipients, and Hyperacute and Delayed Antibody-Mediated Rejection
  - Management of ABO “Incompatible” Heart Transplant Recipients
  - Coagulopathies in Heart Transplant Surgery
  - Documentation and Communication with the Multidisciplinary Team
  - Use of Extracorporeal Membrane Oxygenation for the Management of Primary Graft
  - Reproductive Health After Heart Transplantation
  - Psychosocial and Psychologic Issues Particularly Related to Adherence to Medical Therapy in Heart Transplant Recipients
  - Substance Use & Abuse
  - Endocarditis Prophylaxis After Heart Transplantation
  - Return to Work or School and Occupational Restrictions After Heart Transplantation
  - Return to Operating a Vehicle After Heart Transplantation
  - Family Screening
  - Management of the Transition from Pediatric to Adult Care After Heart Transplantation
  - Principles of Shared Care After Heart Transplantation
  - Travelling After Heart Transplant
  - Emerging Pathogens, Epidemics and Pandemic Considerations for Heart Transplant Recipients
- Task Force 2 discusses the Immunosuppression and Rejection including:
  - Rejection Surveillance
  - Monitoring of Immunosuppressive Drug Levels
  - Principles of Immunosuppression and Recommended Regimens
  - Treatment of Acute Cellular Rejection
  - Treatment of Hyperacute and Antibody-Mediated Rejection
  - Management of Late Acute Rejection
- Task Force 3 addresses the Long-term Care of Heart Transplant Recipients; Management of Complications including:
  - Minimization of Immunosuppression
  - Management of Neurologic Complications After Heart Transplantation
  - Cardiac Allograft Vasculopathy
  - Malignancy After Heart Transplantation
  - Chronic Kidney Disease After Heart Transplantation
  - Management of Cardiovascular Risk After Heart Transplantation
  - Other Complications of Chronic Immunosuppression
  - Arrhythmias
  - Anticoagulation after Heart Transplant
  - Monitoring Recipients of Organs from Donors at Higher Risk of Infectious Diseases
  - Graft Failure & Considerations for Cardiac Retransplantation
- Taskforce 4 covers the Long-term Care of Heart Transplant Recipients. Prevention and Prophylaxis including:
  - Frequency of Routine Tests and Clinic Visits in Heart Transplant Recipients
  - Prophylaxis for Corticosteroid-Induced Bone Disease
  - Exercise, Nutrition and Physical Rehabilitation After Heart Transplantation
  - Management of Intercurrent Surgery in Heart Transplant Recipients

#### International Society for Heart and Lung Transplantation Standards and Guidelines Committee Grading Criteria

Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, and effective
Class II	Conflicting evidence and/or divergence of opinion about the usefulness/efficacy of the treatment or procedure
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy
Class IIb	Usefulness/efficacy is less well established by evidence/opinion
Class III	Evidence or general agreement that the treatment or procedure is not useful or effective and in some cases may be harmful
Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries

#### Task Force 1: Perioperative care of the heart transplant recipient

Chair: Kumud Dhital

Co-Chair: Estela Azeka

Contributing Writers: Monica Colvin, Eugene DePasquale, Marta Farrero, Luis García-Guereta, Gina Jamero, Kiran Khush, Jacob Lavee, CJ Michaud, Jignesh Patel, Stephanie Pouch

## Topic 1: Pretransplant optimization

### *Frailty assessment*

There is an important interplay between frailty and heart failure (HF). Frailty is an independent predictor for the development of HF.<sup>1</sup> However, frailty is also associated with increased mortality and morbidity in the elderly and general HF population. The prevalence of frailty is high in advanced HF patients, accounting for over 30% amongst those referred for advanced HF therapies, including heart transplantation (HT). It is an independent prognostic factor for morbidity and mortality, especially in patients with lower peak oxygen consumption (VO<sub>2</sub>).<sup>2</sup> A variety of methods have been utilized to assess frailty in HF with increasing support for its value in assessing HT patients. Currently, the modified Fried frailty criteria with five physical domains (fatigue, hand grip strength, gait speed, unintended weight loss and physical activity) and additional cognitive assessment (Montreal Cognitive Assessment [MoCA] tool) appears to be a reasonable resource for HT candidates.<sup>3</sup> While frailty is associated with increased morbidity and mortality in patients undergoing ventricular assist device (VAD) implantation and HT, it is also largely reversible following these procedures.<sup>3–5</sup>

### *Nutritional assessment and rehabilitation*

Prevalence of malnutrition in the heart failure population is high and represents an independent predictor of poor outcome and mortality.<sup>6</sup> Pre transplant body mass index (BMI) is a factor that has been shown to correlate with survival post heart transplant. A United Network for Organ Sharing (UNOS) registry study showed the relationship between BMI and post-transplant survival to be U-shaped, with transplant candidates who were underweight (BMI <18.5 kg/m<sup>2</sup>) and candidates who were obese (BMI > 35 kg/m<sup>2</sup>) having significantly decreased survival from year 1 to 5.<sup>7</sup> It is important to note, however, that in regards to nutritional screening and assessment of patients with heart failure, the accuracy of any single nutritional indicator may be compromised by many confounding factors, especially by edema. Edema is caused by fluid retention in addition to inflammatory responses, induced by cytoprotective responses to cellular damage caused by under perfusion of peripheral tissues. Both fluid retention and the inflammatory response affect anthropometric measures such as BMI, triceps skinfold measurement and mid-arm circumference, as well as serum markers, such as albumin and prealbumin. Given secondary confounding factors, multidimensional tools should be used to assess nutrition status.<sup>6,8,9</sup> Based on a systematic review of literature, the most commonly used tools that provide scores that were independent prognostic factors for mortality risk in heart failure patients, were the Mini Nutritional Assessment, MNA-short form, Nutritional Risk Index, and Geriatric Nutritional Risk Index.<sup>9</sup>

Preliminary studies regarding prehabilitation, exercise, and nutrition interventions before surgery have shown

promising results with improved outcomes postsurgery.<sup>10</sup> Interventions may include strategies to (1) improve appetite, such as appetite stimulating agents, including megestrol acetate and anabolic steroids; (2) augment caloric intake, including oral food supplements, or with enteral feedings via nasogastric feeding tube, or percutaneous endoscopic gastrostomy; and (3) directly provide micronutrients, carbohydrates and proteins, such as total parental nutrition.<sup>7</sup> Lastly, post-transplant patients are at high risk for osteopenia and osteoporosis, largely due to use of glucocorticoids and calcineurin inhibitors. Transplant candidates should therefore be evaluated for bone disease by bone marrow density (BMD) and parameters of bone and mineral metabolism, so that appropriate therapies, such as vitamin D supplementation and bisphosphonates, can be initiated to minimize patient's risk for osteopenia following transplant.<sup>11,12</sup>

Cardiac rehabilitation has been shown to improve functional capacity and decrease hospital readmissions in HF patients, and is currently recommended by guidelines.<sup>13,14</sup> Prehabilitation has been shown to decrease post-operative complication after cardiovascular or abdominal surgery.<sup>15,16</sup> Physical activity was related to increased event-free survival on the HT waiting list<sup>17</sup> and better functional capacity and health-related quality of life in heart failure, heart transplant, or left ventricular assist device (LVAD) patients.<sup>18</sup>

### *Psychosocial and behavioral optimization*

Pre-transplant psychosocial factors, including patients' history of medical adherence, mental health, substance use, and social support, can predict outcomes following heart transplantation. Certain factors, such as noncompliance to medical regimen, smoking and alcohol abuse, psychiatric conditions such as depression, and minimal or no social support, have been shown to lead to behaviors of continued or relapse of nonadherence to medical regimen, relapse of substance use, poor self-care, and poor coping. These behaviors lead to poor health-related quality of life with increased morbidity and mortality post-transplant. To maximize outcomes, efforts should be made, before transplant, to optimize factors that are modifiable, based on pretransplant psychosocial evaluation. Interventions may include support groups for substance use, ongoing counseling or therapy, optimization of medical therapy for psychiatric illnesses, and utilization of community resources.<sup>19</sup>

### *Hemodynamic optimization*

The presence of pretransplant pulmonary hypertension (PH) in heart organ recipients increases the risk of post-transplant PH and deterioration in right ventricular function in the donor heart. Large registry studies show pretransplant PH is associated with significantly worse short-term survival post HT compared to patients without pretransplant PH.<sup>20,21</sup> However, assessment of isolated pulmonary hypertension, related to left ventricular failure and reversibility following

**Table 1** Hemodynamic Profiles of Pulmonary Hypertension<sup>a</sup>

Classification	Mean pulmonary artery pressure	Pulmonary capillary wedge pressure	Pulmonary vascular resistance
Isolated pre-capillary PH	>20 mm Hg	<15 mm Hg	>3 WU
Combined pre- and post-capillary PH		>15 mm Hg	>3 WU
Isolated post-capillary PH		>15 mm Hg	<3 WU

WU, wood units.

<sup>a</sup>The 6th World Symposium on Pulmonary Hypertension defined three hemodynamic profiles of pulmonary hypertension (PH): isolated precapillary PH, combined. The pre- and postcapillary PH, and isolated postcapillary PH).<sup>22</sup>

transplant, remains challenging. In 2018, the 6th World Health Symposium on Pulmonary Hypertension developed two main changes in the definition and classification of PH.<sup>22</sup> First, PH is defined by a mean PAP (mPAP) greater than 20 mm Hg (previously greater than 25 mm Hg). The lower parameter reflects recent studies suggesting that individuals with mPAP 21 to 24 mm Hg are at increased risk of poor outcomes and tend to progress to “overt PH” (mPAP 25 or greater) more often than patients with lower mPAP (20 mm Hg or less).<sup>23,24</sup> In addition, PH was further subclassified by pulmonary vascular resistance (PVR) to help stratify pre-capillary PH (as seen in PAH), and isolated post-capillary PH (IpcPH, related to left ventricle (LV) dysfunction, as well as combined pre- and post-capillary PH (CpcPH) (Table 1). While subcategorization and method of detecting CpcPH remains controversial, current evidence suggests that CpcPH is a distinct entity from PAH or IpcPH and carries a different prognosis both before and after HT.<sup>22,25</sup>

Right heart catheterization should be performed on all adult candidates in preparation for listing, and periodically when patients are listed.<sup>26</sup> Strategies to assess and optimize elevated pulmonary artery (PA) pressures should be utilized to determine reversibility in order to prevent right ventricular failure post-transplant. Medical therapies include diuretics, inotropes, and vasoactive agents, both inhaled (i.e., nitric oxide and prostacyclins), and intravenous (i.e., nitroglycerin and nitroprusside). Phosphodiesterase-3 (PDE-3) inhibitors (i.e., milrinone) have shown immediate hemodynamic effects, however, with no long-term effects on clinical outcomes in PH due to LV failure. Other therapies typically used for WHO Group 1 PH (pulmonary arterial hypertension) have been utilized for WHO group 2 PH (due to LV failure) with varying results. PDE-5 inhibitors (i.e., sildenafil) has demonstrated some beneficial effects. Additionally, endothelin receptor antagonists (ERAs) such as bosentan and tezosentan have shown some improvement in hemodynamics in preclinical and small studies albeit with adverse effects, including hepatic dysfunction. Newer ERAs, such as mace-tentan, without adverse effects on hepatic function are currently being studied. Finally, PH refractory to medical therapy has been effectively treated with mechanical

circulatory support, such as LVADs, with improvement in PH and successful bridging to transplant.<sup>27</sup>

### **Consideration of mechanical circulatory support for bridging to transplant**

Patients with HF refractory to optimal medical therapy, with hemodynamic instability and/or progressive end organ dysfunction, should be considered for short-term and/or long-term mechanical circulatory support (MCS). MCS therapy should be directed by the trajectory of HF progression and clinical status.<sup>28–34</sup>

### **Impact of pediatric risk models on wait-list management**

Selection of pediatric recipients is a multifactorial process including specific considerations of factors that will directly impact posttransplant outcome. Furthermore, the spectrum of advanced therapies as well as donor policies, public initiatives and published studies have significantly changed approaches in the management and care of this special population. Candidate selection and waitlist removal are a multidisciplinary process that balances the risks and benefits for the transplant procedure.<sup>35,36</sup>

Pediatric risk factor models have been studied in early and late mortality.<sup>35</sup> Risk factors for early mortality include: recipient variables such as diagnosis, age, gender, sensitization, pulmonary vascular resistance, noncardiac end organ status, mechanical ventilation, extracorporeal membrane oxygenation, VADs; donor-related factors including ischemic time, donor graft function, cause of death. Small center volume has been described as a potential variable for increased post-transplant mortality. A model for in-hospital mortality after pediatric transplantation has been studied using variables available in Organ Procurement Transplantation Network (OPTN) which includes hemodynamic support; Extracorporeal Membrane Oxygenation (ECMO), VAD, ventilator and medical therapy, cardiac diagnosis, renal dysfunction, and serum total bilirubin. This model has C-statistics of 0.75 and 0.81.<sup>37</sup> The risk factor model using donor variables on 1-year or late mortality post-transplant has been studied using the

OPTN registry<sup>38</sup> including ischemic time, stroke as the cause of death, donor-to recipient height ratio, donor left ventricular ejection fraction, and donor glomerular filtration rate. This model can be useful when assessing acceptability of a prospective organ in a recipient. Therefore, risk factors models can provide an impact on wait list management after acknowledgement of unmeasured and confounding factors.

### ***Nutritional assessment, nutritional rehabilitation, and nutritional interventions in the pediatric population***

Nutritional status in most pediatric chronic conditions is a major determinant of childhood well-being. Chronic HF in children is a major cause of malnutrition.<sup>39–43</sup> Malnutrition is an imbalance of nutrients between intake and nutritional requirements. The body is unable to meet metabolic demands in the setting of cardiac dysfunction. The pathophysiology of heart failure involves activation of compensatory pathways, proinflammatory cytokines, neurohormonal abnormalities, increased metabolic demands, reduced intake, and malabsorption.<sup>44</sup> These mechanisms lead to starvation, malabsorption nutritional loss, and hypermetabolism which result in malnutrition and suboptimal growth. Therefore, it is recommended that nutritional status should be addressed by history, and nutritional and physical assessment. The basic tools for initial evaluation include a history of energy, protein and fluid intake, weight, length, head circumference measurements on sex- and age-specific growth curves<sup>44,45</sup> (weight for age, length for age, body mass index) on which individual patient's values can be plotted and detection of growth velocity deviation. Nutritional support includes hypercaloric feeds, oral supplements, and enteral and parenteral nutrition. Enteral nutrition is required when oral intake is insufficient. Conditions such as severe cord dysfunction, dysphagia, or oral aversion can interfere with adequate oral intake. Nasojejunal tube feeds may be used when nasogastric tube feeds are not tolerated. Nutritional support via gastrostomy can be effective at reversing malnutrition, in maintaining nutritional status, and may be indicated in children requiring prolonged enteral tube feeding. Multidisciplinary discussions surrounding the risk of surgical intervention and anesthesia are required in these cases.

### ***Consideration of bridge to transplant with MCS in pediatric recipients***

The use of VADs in pediatric patients for the treatment of advanced HF has increased significantly in the past decade and has supplanted ECMO as the most common form of MCS as a bridge to HT. The percentage of children with MCS as a bridge to transplantation has increased from 25% in 2010 to 36% in 2019. The majority of MCS implants in the pediatric population are INTERMACS profiles 1 or 2 with significantly decreased waitlist mortality. However, the ISHLT registry data demonstrates no survival difference between children with or without VAD support, except for worse outcomes in those bridged with ECMO.<sup>46–49</sup>

### ***Pretransplant vaccinations in adult and pediatric candidates for heart transplantation***

There are limited data specifically addressing vaccination of adults and children with advanced HF in the pre-transplant setting.<sup>26,41,50–53</sup>

#### Topic 1: Pretransplant Optimization

2010 Prior Guideline Recommendation	2023 Update Guideline Recommendation
<b>New Recommendation</b>	Assessment of frailty using the modified Fried's criteria (3 of 5 possible symptoms, including unintentional weight loss of >10 pounds within the past year, muscle loss, fatigue, slow walking speed, and low levels of physical activity) should be considered when assessing candidacy. <b>Class I, Level of Evidence C</b>
<b>New Recommendation</b>	Multidimensional nutritional assessment tools should be used to evaluate heart transplant candidates for malnutrition or for being at risk for malnutrition. <b>Class I, Level of Evidence C</b>
<b>New Recommendation</b>	Cardiac rehabilitation is reasonable in patients awaiting heart transplantation in order to decrease readmissions, wait list mortality and improve post-transplant outcomes. <b>Class IIa, Level of Evidence C</b>
<b>New Recommendation</b>	Various interventions, such as oral/enteral supplementation, appetite stimulants, micronutrient replacement, and anabolic steroids may be beneficial in optimizing nutritional status before transplant to help decrease adverse outcomes including mortality post transplant. <b>Class IIa, Level of Evidence C</b>
<b>New Recommendation</b>	Based on psychosocial and behavioral evaluation at time of heart transplant evaluation, interventions and therapies should be initiated to address psychosocial and behavioral risk factors that may contribute to poor outcomes post-transplant. <b>Class I Level of Evidence C.</b>
<b>New Recommendation</b>	A vasodilator challenge should be administered when the pulmonary artery systolic pressure is $\geq 50$ mm Hg and either the transpulmonary gradient is $\geq 15$ or the pulmonary vascular resistance (PVR) is $> 3$ Wood

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## Topic 1: Pretransplant Optimization

2010 Prior Guideline Recommendation	2023 Update Guideline Recommendation
	units while maintaining a systolic arterial blood pressure > 85 mm Hg. <b>Class I, Level of Evidence C</b>
<b>New Recommendation</b>	When an acute vasodilator challenge is unsuccessful, hospitalization with continuous hemodynamic monitoring should be performed, as often the PVR will decline after 24 to 48 hours of treatment consisting of diuretics, inotropes, and vasoactive agents, including inhaled nitric oxide. <b>Class I, Level of Evidence C</b>
<b>New Recommendation</b>	Following bridging left ventricular assist device (LVAD) implantation, re-evaluation of hemodynamics, particularly in respect of the Trans-Pulmonary Gradient (TPG) and PVR is reasonable to be done after 3 months and at regular intervals thereafter to ascertain reversibility of pulmonary hypertension. <b>Class IIa, Level of Evidence C</b>
<b>New Recommendation</b>	If medical therapy fails to achieve acceptable hemodynamics, and if the left ventricle cannot be effectively unloaded with mechanical adjuncts, including an intra-aortic balloon pump (IABP) and/or mechanical circulatory support (MCS), it may be reasonable to conclude that the pulmonary hypertension is irreversible. <b>Class IIb, Level of Evidence C</b>
<b>New Recommendation</b>	IABP and short-term MCS should be considered in patients in cardiogenic shock refractory to medical therapy until hemodynamic parameters and end organ function are stabilized, followed by further consideration of urgent HT or continued +/- upgrade to longer-term MCS as deemed appropriate. <b>Class I, Level of Evidence C</b>
<b>New Recommendation</b>	Long-term MCS should be considered in patients: (a) When ventricular function is unlikely to recover soon or has been deemed unrecoverable. (b) Who are inotrope dependent and therefore at high risk for death with ongoing medical management. (c) Who are potential HT candidates, with elevated pulmonary vascular resistance that is considered reversible with left ventricular (LV) decompression.

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## Topic 1: Pretransplant Optimization

2010 Prior Guideline Recommendation	2023 Update Guideline Recommendation
	(d) Who are potential HT candidates, with contraindications requiring substantial time to reverse, i.e., cancer, obesity, drug and/or alcohol dependence. (e) With a reversible cardiac disease process that requires substantial time for ventricular recovery. (f) Who are ineligible for HT and where long-term MCS is an option. <b>Class I, Level of Evidence C</b>
<b>New Recommendation</b>	Pediatric risk models may be reasonable to assist with pediatric wait-list management including the removal of patients who are too sick to undergo and benefit from HT. <b>Class IIb, Level of Evidence B</b>
<b>New Recommendation</b>	Pediatric transplant recipients plotting below the third percentile (−2 standard deviation) can benefit from further assessment, referral, or intervention for nutrition support. <b>Class IIa, Level of Evidence C</b>
<b>New Recommendation</b>	Consideration should be given to address moderate or severe wasting and an elevated weight/height as these findings are independent risk factors for waitlist mortality in young patients aged 0-2 years despite the fact there is no apparent effect of these conditions on post-HT mortality. <b>Class IIa, Level of Evidence C</b>
<b>New Recommendation</b>	Energy and nutrient intake and barriers to intake are reasonable to assess at regular intervals. <b>Class IIa, Level of Evidence C</b>
<b>New Recommendation</b>	The decision to insert a gastrostomy tube is reasonable to be determined by a multidisciplinary team through a holistic consideration of medical, ethical, psychological, and quality-of-life issues. <b>Class IIa, Level of Evidence C</b>
<b>New Recommendation</b>	Temporary MCS should be considered for potential or actual transplant candidates at high risk of mortality with medical management alone <b>Class I, Level of Evidence C</b>
<b>New Recommendation</b>	Temporary MCS devices permit a longer duration of hemodynamic assistance with superior patient survival when compared to conventional

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## Topic 1: Pretransplant Optimization

2010 Prior Guideline Recommendation	2023 Update Guideline Recommendation
	Extracorporeal Membrane Oxygenation (ECMO) therapy. Therefore, MCS should be considered as bridging therapy to pediatric HT in the case of refractory heart failure <b>Class I, Level of Evidence A</b>
<b>New Recommendation</b>	Bridging ventricular assist device (VAD) rather than ECMO support should be considered in children for better survival to HT. <b>Class I, Level of Evidence C</b>
<b>New Recommendation</b>	Based on current technology and availability, paracorporeal devices are recommended for children smaller than 20-25 kg. <b>Class I, Level of Evidence C</b>
<b>New Recommendation</b>	ECMO support may be used as a bridge to decision-making, as a bridge to VAD therapy, or as a bridge to transplantation in critical situations. <b>Class IIa, Level of Evidence C</b>
<b>New Recommendation</b>	Pediatric heart failure patients $\leq 24$ months of age and who meet criteria for respiratory syncytial virus prophylaxis should receive palivizumab in accordance with established guidelines. <b>Class I, Level of Evidence A</b>
<b>New Recommendation</b>	Vaccine history and assessment of seroprotection (as appropriate) should be reviewed before listing for heart transplantation. Transplant candidates who are unvaccinated or incompletely vaccinated should receive recommended vaccinations as early as possible, as end-organ failure and iatrogenic immunosuppression may diminish vaccine responses. <b>Class I, Level of Evidence C</b>
<b>New Recommendation</b>	In most situations, live virus vaccines are contraindicated following transplantation. Every attempt should be made to complete live virus vaccines, including MMR, varicella, live attenuated zoster, and rotavirus, before transplantation in non-immune patients according to established guidelines. Live virus vaccination should ideally be completed four weeks before transplantation. <b>Class I, Level of Evidence C</b>

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## Topic 1: Pretransplant Optimization

2010 Prior Guideline Recommendation	2023 Update Guideline Recommendation
<b>New Recommendation</b>	Before transplantation, candidates should receive inactivated vaccines, including but not limited to influenza, pneumococcal, tetanus, pertussis, hepatitis A and B, and human papillomavirus vaccines, in accordance with established guidelines. Inactivated vaccines should ideally be completed two weeks before transplantation. <b>Class I, Level of Evidence C</b>
<b>New Recommendation</b>	The recombinant subunit zoster vaccine is preferred over the live-attenuated vaccine for transplant candidates and should be given in accordance with local vaccination guidelines. <b>Class IIa, Level of Evidence C</b>

**Topic 2: Surgical issues impacting care in the immediate Postoperative period*****Transplantation of hearts from donors with infection***

Donor-derived disease transmissions are uncommon. However, the decision to utilize organs from donors with documented infection should be made with involvement of the transplant infectious diseases team. The use of organs from hepatitis C viremic donors has been associated with excellent short-term outcomes in HT recipients.<sup>54–57</sup>

Transmissions of leukemia, lymphoma, rabies, and other central nervous system infections have been reported from donors with encephalitis of unknown etiology, and such donors should be avoided.<sup>57</sup>

***Transplantation of hearts from donors with potential drug toxicities***

While small single center studies have shown conflicting results with donor use with various drug toxicities in heart transplantation, large retrospective registry studies have demonstrated that use of donors with history of alcohol abuse, cocaine use (active or past), or drug overdose does not have deleterious effects on short- and long-term survival post HT.<sup>58–63</sup> Several case studies show successful transplantation with donors who suffered carbon monoxide poisoning. While safety is not completely established, the use of hearts in these donors can reasonably be considered in the setting of clinical and objective evidence of satisfactory cardiac function.<sup>64–66</sup>



**Use of donors with pre-existing cardiac abnormalities**

There is data limited to small studies and case reports regarding the use of donors with coronary artery disease (CAD) that demonstrate varying results and effects of donor CAD on post-transplant vasculopathy and overall outcomes.<sup>67–70</sup> The presence of aortic valve disease (stenosis or insufficiency) in the absence of either LV dilatation or LV hypertrophy should not preclude donor consideration. Isolated cases of aortic or mitral valve intervention at the time of heart transplant have been performed with acceptable outcomes. However, this consideration should be balanced with risks and benefits for the recipient.<sup>71–74</sup> Use of donor heart with a secundum atrial septal defect (ASD) can be used with backbench repair of the ASD before implanting the donor heart.<sup>75</sup> Use of donors with left ventricular hypertrophy (LVH) remains controversial. Small retrospective studies have shown mixed results. Recent registry analysis demonstrated that almost half of all used donors had LVH (interventricular septum or left ventricular posterior wall thickness ≥ 1.1 cm), with 5.6% having moderate to severe LVH (≥ 1.4 cm). This study demonstrated similar survival up to 3 years post-transplant regardless of the presence of LVH. However, donors with LVH and additional factors (≥ 55 years old or ischemic time > 4 hours) led to significantly worse 3-year survival. A 2017 consensus conference identified LVH as one of the most important risk factors to consider when evaluating donor organs, with approximately half the participants stating that an organ with LVH greater than 1.3 cm would be considered as unacceptable.<sup>76,77</sup>

**Donor cardiac function**

Multiple large retrospective registry studies have demonstrated that donor hearts with initial low EF may have reversible dysfunction particularly in the setting of younger age or brain death/ severe brain injury causing neurogenic stress cardiomyopathy. In the case of brain death/injury, donor management recommendations include hormonal replacement (i.e., thyroxine and steroids), optimization of cardiac loading conditions (i.e., diuretics, vasopressors), and catecholamine repletion (i.e., inotropes). Donor hearts with initial low EF that improve have been utilized with no significant difference in short- and long-term survival compared to donors with normal initial EF ≥55%. Systolic function of these donor hearts may continue to improve post transplantation. Thus, donor hearts with initial low EF that improve with appropriate donor management should be considered for transplantation.<sup>76–81</sup>

**Donor-recipient size matching**

Multiple large registry studies have shown predicted heart mass to be the optimal metric for size matching donor and recipient in heart transplant. The degree of undersizing or oversizing by predicted heart mass correlates more accurately with survival post-transplant compared to weight alone though prospective studies are warranted (Table 2).<sup>82–85</sup>

**Donor considerations for pediatric recipients**

Recommendations relevant to pediatric donor considerations are presented in the ISHLT Pediatric Consensus statement.<sup>55</sup>

**Recommendations on the utilization of donation after circulatory death donor hearts**

Since the successful introduction of utilizing distantly procured donation after circulatory death hearts into clinical practice in 2014, with the necessary and adjunctive use of organ perfusion technology, donation after circulatory death (DCD) heart transplantation has become standard of care in several transplant centers in Australia and the United Kingdom.<sup>86,87</sup> Excellent early- and medium-term outcomes have encouraged a wider uptake across some European centers and led to the initiation of the FDA approved *Donors after Circulatory Death Heart Trial* (NCT03831048) across 25 institutions in the US that is expected to complete in December 2021.<sup>88</sup> To date over 270 DCD heart transplants have been performed with outcomes that are non-inferior to heart transplants from standard care hearts from donation after brain death (DBD) donation. Clinical outcomes to date, from utilizing a significant new pool of donor hearts warrants recommendation for the controlled use of DCD hearts.

**Recommendations on the perioperative management of the multiorgan recipient**

*Heart/Kidney.* Perioperative management of simultaneous heart-kidney transplant (SHKT) entails management of intraoperative hemodynamics by avoiding hypotension and hypovolemia – major factors contributing to delayed kidney graft function. Use of inotropes, vasopressors, and volume repletion as needed should be used to maintain adequate blood pressure and avoid volume depletion. Patients with arteriovenous (AV) fistula are at risk for left-to-right shunting causing increased cardiac output and decreased diastolic pressure, leading to right ventricular

**Table 2** Predicted Heart Mass Calculator (Internet-Based Calculator Application – <https://transplanttoolbox.shinyapps.io/calcpfm>)<sup>82</sup>

Predicted right ventricular mass(RVM)	$a \times \text{Age}^{-0.32} \times \text{Height}^{1.135} \times \text{Weight}^{0.315}$ where a = 10.59 for women and 11.25 for men
Predicted left ventricular mass(LVM)	$a \times \text{Height}^{0.54} \times \text{Weight}^{0.61}$ where a = 6.82 for women and 8.25 for men
Predicted heart mass (PHM)	RVM + LVM
Body mass index (BMI)	$\frac{\text{Weight}}{\text{Height}^2}$
Body surface area (BSA)	$a \times \text{Height}^{0.725} \times \text{Weight}^{0.425}$ where a = 0.007184
Donor to recipient size match	$\frac{\text{Size metric}_{\text{donor}}}{\text{Size metric}_{\text{recipient}}}$

distension and compromised coronary perfusion during and after weaning from cardiopulmonary bypass.<sup>89</sup> Temporary closure of AV fistula with an inflatable cuff can help prevent excessive flow from shunt and deleterious effects, and allow successful weaning off bypass.<sup>90</sup> Post heart transplant, but before and during the kidney transplant procedure requires management of a hyperdynamic, vasodilatory state (vasodilation due to inflammatory response with CPB, ischemia-reperfusion injury, and surgical trauma).<sup>91</sup> Surgical sequence is still a matter of debate. Staged sequence refers to the allowance of perioperative recovery and hemodynamic stabilization following heart transplantation in the ICU, with subsequent return to the OR for kidney transplantation. Non-staged sequence is defined as when heart transplantation is followed by kidney transplantation within the same operation and permits a shorter ischemic time for the kidney graft.<sup>91</sup> Optimal induction and long-term immunosuppression remains to be determined by further studies. A recent UNOS Registry study suggested r-ATG may provide survival benefit in SHKT, especially in sensitized patients, eventually maintained on tacrolimus, mycophenolate mofetil, and prednisone.<sup>92,93</sup>

### **Recommendations on the perioperative management of the multiorgan recipient**

**Heart/Liver.** Combined heart liver transplantation is slowly increasing in frequency, predominantly performed for cardiomyopathy and liver disease as a consequence of familial amyloid or congenital heart disease.<sup>93,94</sup> Various single center and registry studies demonstrate favorable patient survival and graft survival with combined heart-liver transplantation as well as decreased rejection compared to heart transplant alone.<sup>95</sup> It appears to be an immunoprotective effect of liver transplant in dual organ transplant. Mechanisms are not clearly understood, but it has been postulated that absorption of alloreactive immune complexes by the

large surface area of the liver results in decreased donor specific antibodies. Immunosuppression protocols may therefore theoretically be reduced in combined heart-liver transplant rather than based on protocols for solitary organ recipients and could potentially decrease the risk of infection. From a surgical standpoint, heart transplant is typically performed first followed by liver transplant. Liver transplant may be performed within the same operation with a chest open while the heart is reperfused on cardiopulmonary bypass. Once liver transplantation is completed, CBP may be weaned off and the chest closed. If needed, liver transplant may be delayed until after stabilization of hemodynamics in the ICU following heart transplant. Liver transplant can be performed using standard caval interposition or piggyback technique, and selective use of veno-venous bypass. En-bloc technique has also been utilized in which both heart and liver are simultaneously implanted on cardiopulmonary bypass, and subsequently reperfused simultaneously. Finally, reverse sequence of transplants has been reported, entailing liver transplant performed before heart transplant. This sequence has been performed in sensitized patients with high donor specific antibodies, in order to allow the "immunoprotection" of the liver to take effect before implantation of the donor heart.<sup>93–95</sup> Management of this complex cohort of patients requires close multidisciplinary collaboration of both heart and liver transplant teams, from patient selection, donor evaluation, surgical planning, and postoperative care, particularly regarding immunosuppression.<sup>96</sup>

### **Topic 3: Considerations in patients bridged with MCS**

The number of heart transplant patients that have been bridged to transplant with MCS devices has increased over

#### **Topic 2: Surgical Issues Impacting Care in the Immediate Postoperative Period**

##### **2010 Prior Guideline Recommendation**

Taking into consideration only the variable of "donor age," the hearts of donors younger than 45 years will invariably have sufficient reserves to withstand the rigors of heart transplant (HT) even in settings of prolonged ischemic time, recipient comorbidities, and multiple previous recipient operations with hemodynamically destabilizing bleeding. Hearts from donors between the ages of 45 and 55 years should probably be used when the projected ischemic time is  $\leq 4$  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

##### **2023 Update Guideline Recommendation**

Continuing approval without change.

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## Topic 2: Surgical Issues Impacting Care in the Immediate Postoperative Period

## 2010 Prior Guideline Recommendation

unequivocally exceeds the decrement in early HT survival due to transplantation of a heart with limited myocardial reserves.

Class IIa, Level of Evidence B.

**New Recommendation**

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.

Class IIa, Level of Evidence C.

**New Recommendation****New Recommendation****New Recommendation**

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.

Class IIa, Level of Evidence C

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.

Class IIa, Level of Evidence C

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,

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Hearts from donors with risk factors for acute HIV, hepatitis B, and hepatitis C infection are safe for transplantation, and recipients should be informed, monitored and treated where appropriate in accordance with established guidelines.

**Class I, Level of Evidence B**

Hearts from donors with **known bacteremia** can be used provided that (1) the donor has **received 24-48 hours of targeted antimicrobial therapy, ideally with clearance of cultures**, (2) donor myocardial function is normal, (3) there is no evidence of endocarditis upon direct inspection of the donor heart. **Recipients of hearts from bacteremic donors should receive an appropriate course of antimicrobial therapy targeting the donor isolate. Transplant Infectious Diseases should be involved in all cases of donor bacteremia, particularly when the donor isolate is multidrug-resistant.**

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

Hearts from donors with bacterial meningitis can be used provided the donor has received 24-48 hours of targeted antimicrobial therapy and the recipient receives an appropriate course of targeted therapy following transplantation.

**Class IIa, Level of Evidence C**

Hearts from donors with positive hepatitis C viremia may be used provided HCV-specific informed consent is obtained from the recipient and the recipient is monitored and treated in accordance with established guidance.

**Class IIa, Level of Evidence B**

Hearts from donors with encephalitis of unclear etiology should not be used for transplantation.

**Class III, Level of Evidence C**

Continuing approval without change.

Use of hearts from donors with history of alcohol abuse, active or past use of cocaine, and drug overdose can be considered.

**Class IIa, Level of Evidence C**

Use of hearts from donors who have died of carbon monoxide intoxication can be recommended with caution, although safety not completely established.

**Class IIa, Level of Evidence C**

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## Topic 2: Surgical Issues Impacting Care in the Immediate Postoperative Period

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minimal inotropic requirements, a relatively short ischemic time, a favorable donor to recipient weight ratio and a recipient with normal pulmonary vascular resistance.  
Class IIa, Level of Evidence C

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

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.  
Class I, Level of Evidence C

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 by Class IIa, Level of Evidence C pass surgery.

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.  
Class IIa, Level of Evidence C

**New Recommendation****New Recommendation****New Recommendation**

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.  
Class I, Level of Evidence C

Continuing approval without change.

Continuing approval without change.

The use of higher risk donor hearts with obstructive disease in any major coronary artery should be avoided unless the heart is being considered with concomitant coronary bypass surgery for a recipient who is marginal, older or at risk of imminent death.  
**Class IIa, Level of Evidence C**

Use of donor organs with LV septal or posterior wall thickness >13mm should be used with caution, especially in conjunction with other high-risk characteristics such as age  $\geq$  55 years and an allograft ischemic time >4 hours.  
**Class IIa, Level of Evidence C**

Donor hearts with an initial low EF should be evaluated for possible reversible causes of dysfunction, particularly in the setting of a younger age donor following severe brain injury.  
**Class IIa, Level of Evidence C**

Optimizing donor heart function with hormonal replacement, hemodynamic optimization, and catecholamine repletion is reasonable.  
**Class IIa, Level of Evidence C**

If EF improves with optimization measures, donor heart can be considered for transplantation.  
**Class IIa, Level of Evidence C**

Continuing approval without change.

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## Topic 2: Surgical Issues Impacting Care in the Immediate Postoperative Period

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**New Recommendation**

Using the predicted heart mass (PHM) calculation to aid in matching donor and recipient is reasonable. A donor/recipient PHM ratio 0.86 or greater is reasonable to proceed with transplant. A donor/recipient PHM ratio from 0.86 to 0.7 may be considered for individual cases however, a PHM ratio less than 0.86 may be associated with adverse post-transplant outcomes.

**Class IIa, Level of Evidence C**

**New Recommendation**

Generally, the use of undersized or oversized hearts needs to be carefully considered when making decision for donor-recipient mismatch.

**Class IIa, Level of Evidence B**

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

Class I, Level of Evidence C

Generally, the ischemic time should be less than 4 hours. However, donor hearts with ischemic times longer than 4 hours may be utilized when other risk-compounding factors are ideal including: favorable age and size matching; normal cardiac function; and absence of significant inotropic and vasopressor support.

**Class I, Level of Evidence C**

**New Recommendation**

The use of Donation after Circulatory Death (DCD) hearts is reasonable at centers with: experience using marginal donor hearts, familiarity with the use of *ex situ* organ perfusion devices for preservation and transportation, and experience instituting peri-operative mechanical support and its after-care for possible primary graft dysfunction.

**Class IIa, Level of Evidence C**

**New Recommendation**

During simultaneous heart-kidney transplant (SHKT), to maintain optimal renal perfusion, careful attention should be given to hypotension and hypovolemia with use of inotropes/vasopressors and maintain adequate volume status using hemodynamic parameters.

**Class IIa, Level of Evidence C**

**New Recommendation**

Time allowed for hemodynamic stabilization following heart transplant, before kidney transplant, should be balanced with prolonged ischemic time of the kidney graft.

**Class IIa, Level of Evidence C**

**New Recommendation**

Multidisciplinary meetings with the heart and liver transplant teams should be held to plan for donor, operative, immunosuppression considerations before transplantation.

**Class I, Level of Evidence C**

**New Recommendation**

Efforts to prevent acute RV dysfunction with minimization of blood products and volume given during liver transplant may be reasonable. Massive fluid resuscitation can overload the RV, induce progressive RV dysfunction and precipitate or worsen tricuspid valve regurgitation.

**Class IIb, Level of Evidence C**

**New Recommendation**

With the observed immunoprotective effect of liver transplant in dual organ transplants, reduced immunosuppression protocols may be considered in carefully selected heart-liver transplant recipients.

**Class IIb, Level of Evidence C**

the last decade, and now accounts for approximately 50% of heart transplants per year according to the ISHLT Registry. Most data suggest no significant decrement in survival among recipients bridged to transplant with durable LVAD compared to recipients medically managed before transplant. However, LVAD complications convey higher risk, particularly those with device-related infection showing significantly higher mortality risk post-transplant.<sup>97</sup> Patients bridged with temporary LVAD or biventricular MCS had no difference in survival within 1 year compared to continuous flow LVAD (CF-LVAD) in an ISHLT registry analysis. Bridging with temporary biventricular VAD or ECMO support generally demonstrated decreased survival post-transplant, but this risk may be acceptable when compared to the significant risk of waitlist attrition without bridging mechanical support.<sup>97</sup>

Most research has focused on durable continuous flow left ventricular assist devices (CF-LVAD) implanted as bridge to transplant. Studies have demonstrated various patient and donor risk factors for post-transplant mortality in varying degrees of significance in this population. An ISHLT Registry analysis<sup>98</sup> demonstrated that the strongest risk factors for 30-day mortality in patients bridged with continuous flow LVADs were ventilator support at time of transplant, female recipient/male donor (compared to other combinations), history of hemodialysis, and history of CABG. Other factors included increasing recipient age, body mass index, creatinine, and total bilirubin, as well as increased pulmonary artery diastolic pressure with decreased wedge pressure. More recently, a matched cohort study utilizing the UNOS Registry<sup>99</sup> demonstrated that patients bridged with CF-LVAD had lower early survival at 1 year compared to medically managed patients who underwent heart transplant. Risk factors of LVAD patients for 1 year post transplant mortality were: LVAD support duration > 6 months, eGFR 40 to 60 mL·min<sup>-1</sup> 1.73 m<sup>2</sup>, BMI >30kg/m<sup>2</sup>, and PVR > 2 Wood units. However, five-year survival, conditional on one year survival, demonstrated no difference between the groups.

Following heart transplantation, patients bridged with MCS are at higher risk for primary graft dysfunction and vasoplegia. Vasoplegia presenting as low cardiac output refractory to catecholaminergic drugs with severe hypotension requiring vasopressors for maintenance of blood pressure. Possible mechanisms linking BTT LVAD and PGD<sup>99</sup> include occult subclinical right ventricular dysfunction from prolonged LVAD support, longer ischemic and cardiopulmonary bypass time with redo sternotomy and removal of device, and extensive bleeding secondary to chronic anticoagulation requiring multiple transfusions.<sup>99</sup> Possible mechanisms leading to vasoplegia<sup>99</sup> include a chronic inflammatory response related to the device due to contact of blood with synthetic surfaces. Vasoplegia may also be caused by endothelial dysfunction from prolonged continuous flow with subsequent vasoreactivity changes in peripheral vasculature.<sup>100</sup>

### Topic 3: Considerations in Patients Bridged With MCS

2010 Prior Guideline Recommendation	2023 Update Guideline Recommendation
<b>New Recommendation</b>	MCS as bridge to transplant should be considered for potential transplant candidates with high risk of mortality with medical management alone. <b>Class I, Level of Evidence C</b>
<b>New Recommendation</b>	Any decrease in survival that may be attributable to MCS devices, should be weighed against risk of mortality on the waiting list without MCS, and whether a reasonable post-transplant survival appears achievable. <b>Class I, Level of Evidence C</b>
<b>New Recommendation</b>	Patient, donor, and device-related risk factors that have been associated with increased morbidity and mortality post heart transplantation, should be carefully considered collectively when accepting a donor organ and deciding to proceed with transplantation. <b>Class I, Level of Evidence C</b>

### Topic 4: Early postoperative care of the heart transplant recipient

#### *Treatment of Postoperative vasoplegia*

Reduction in vascular tone after heart transplant is postulated to occur due to a general inflammatory response to CPB and dysregulation of the cGMP-NO pathway. Risk factors for vasoplegia include the following: older recipient age, longer period of LVAD support, impaired renal function, prolonged CPB time, and prolonged ischemic time.<sup>101, 102</sup> Vasoplegia can be severe and refractory to conservative therapy and is associated with increased morbidity. The underlying mechanism may be related to increased nitric oxide synthesis, which stimulates guanylatecyclase leading to cGMP production with subsequent vascular relaxation. There are case reports<sup>101, 103–106</sup> of successful treatment of post-HT vasoplegia with a single dose of methylene blue, temporary ECMO support, and oral droxidopa and hydroxocobalamin. Treatment of vasoplegia involves titrating vasopressors to improve vascular tone and restore adequate perfusion pressure. Norepinephrine is considered the first-line agent for treatment of vasoplegia, followed by vasopressin and then only a single dose of methylene blue. Other vasoactive medications include epinephrine, dopamine and oral midodrine.<sup>101–110</sup>

### Medical management of right ventricular dysfunction and pulmonary vascular hypertension after heart transplantation

Management of RV dysfunction and pulmonary hypertension focus on optimizing preload and contractility while reducing pulmonary vascular resistance (RV afterload). Patients should be treated with inotropic support (such as epinephrine and isoproterenol) to enhance contractility. Milrinone also helps reduce afterload and pulmonary hypertension. Other agents that reduce pulmonary vascular resistance include inhaled nitric oxide and inhaled prostacyclin or epoprostenol, which have minimal effect on systemic arterial pressures.<sup>108, 111–118</sup>

### Perioperative management of cardiac arrhythmias in heart transplant recipients

AV conduction disorders are common after transplant, affecting more than 10% of HT recipients.<sup>119</sup> They are mainly related to longer surgical times and biatrialanastomosis.<sup>120</sup> AV pacing post-transplant may be performed through epicardial leads and needed to maintain a HR >90 bpm. According to ESC and ACC/AHA/HRS guidelines, pacemaker implant is indicated if symptomatic bradycardia persists after 3 weeks post-transplant.<sup>121, 122</sup> Tachyarrhythmias are also common after HT and can be related to rejection or cardiac allograft vasculopathy (CAV), which need to be excluded.<sup>123</sup> Beta blockers, calcium antagonists, adenosine and amiodarone<sup>124</sup> can be used safely after HT as well as catheter ablation.<sup>125</sup> Amiodarone and calcium antagonists can increase calcineurin inhibitor (CNI) levels. Therefore, CNI dose adjustment and level monitoring are required. Use of adenosine post-transplant was previously a relative contraindication due to presumed risk of prolonged AV block in the denervated heart. However, a recent study suggests minimal risk when low initial doses are used (25 mcg/kg; 1.5 mg if  $\geq$  60 kg) and therapy is gradually increased.<sup>126</sup> Finally, ICD implantation in recipients with severe allograft vasculopathy may mitigate the high risk of sudden cardiac death in this cohort.<sup>127</sup>

### Timing of ICD removal

ICD and/or CRT are common in HT candidates. Lead removal is usually performed at the time of transplant, but a significant number of patients (24–42%) show retained leads after transplant. Those leads are related to an increased prevalence of venous thrombosis and MRI contraindications.<sup>121, 127–130</sup>

### Perioperative management of hyperglycemia in heart transplant recipients

Hyperglycemia is present in 60 to 80% of cardiac surgical patients and is associated with worse outcomes including increased wound infections, acute renal failure, longer hospitalization, and higher perioperative mortality. In heart

transplantation, the three main driving factors for hyperglycemia are: pretransplant diabetes, stress-induced hyperglycemia, and catecholamine/corticosteroid use. Based on observational and randomized controlled studies in critical care and cardiac surgery,<sup>131</sup> maintaining a target glucose level below 180 mg/dL during surgery and in the postoperative period is recommended by most scientific societies.<sup>132, 133</sup> Non diabetic patients could benefit from more strict control: <140 mg/dL. More intense control is associated with lower risk of infection, however, without clear mortality benefit.<sup>131</sup>

### Antibacterial prophylaxis/treatment

The most common pathogens causing surgical site infections in heart transplant recipients are coagulase-negative *Staphylococci* and *S. aureus* (MRSA and MSSA), though other pathogens including gram negatives and *Candida* spp are also encountered. Given the paucity of data specifically addressing perioperative bacterial prophylaxis for heart transplantation, a first-generation cephalosporin with or without vancomycin is commonly used for cardiac surgical procedures and transplantation. Perioperative prophylaxis in patients with device-related infection (i.e., LVAD infection; infection/colonization of an ECMO circuit), should target the implicated pathogens with duration dependent upon the extent of infection. Use of antibacterial prophylaxis in the setting of open chest should be tailored to the clinical scenario.<sup>134–137</sup>

### Perioperative antiviral prophylaxis in heart transplant recipients

The CMV serologic status of the donor and recipient should be used to stratify the risk of post-transplant CMV infection, and antiviral prophylaxis is recommended over preemptive therapy for high-risk mismatches (D+/R-) (Table 3). There are conflicting data regarding the use of antiviral prophylaxis for EBV. While the use of antivirals

**Table 3** Recommendations for the Prevention of Cytomegalovirus in Heart Transplant Recipients

Group	Recommendations
D+/R-	Ganciclovir 5mg/kg IV daily or valganciclovir 900 mg po daily* for 3-6 months Preemptive therapy generally not preferred but is an alternate option Some HT centers will add CMV immune globulin for high-risk patients
R+	Ganciclovir 5mg/kg IV daily or valganciclovir 900 mg po daily* for 3 months Preemptive therapy is an alternate to universal antiviral prophylaxis

may delay the onset of EBV viremia, routine implementation of antiviral prophylaxis is controversial, and pre-emptive monitoring of D+/R- recipients could be considered.<sup>137–144</sup>

### **Perioperative antifungal prophylaxis in heart transplant recipients**

There is a lack of clear data supporting the use of routine anti-Candida prophylaxis in heart transplant recipients with low incidence of invasive candidiasis following transplant.

Risk factors for invasive aspergillosis following transplantation include airway colonization with *Aspergillus* spp., reoperation, post-transplant hemodialysis, need for ECMO, CMV disease, presence of *Aspergillus* spores in the ICU in which heart transplant recipients reside, and development of invasive aspergillosis in any patient with the heart transplant program 2 months before or after the date of heart transplantation. In patients with these risk factors, targeted antifungal prophylaxis may be considered, though the optimal duration is unclear. The risk of *Pneumocystis jiroveci* (PJP) infection is highest within the first 6 months of transplant, but certain risk factors, including prolonged use of high-dose corticosteroids (CS), may augment the risk of PJP. The incidence of coccidioidomycosis among solid organ transplant recipients residing in endemic regions ranges between 1.4 and 6.9%. Most infections occur within the first year of transplant, but azole prophylaxis reduces the risk for post-transplant coccidioidomycosis. Donor-derived *Coccidioides* infection has also been described.<sup>145–159</sup>

### **Perioperative antiprotozoal prophylaxis and treatment in heart transplant recipients**

Transmission of *Toxoplasma gondii* is of greatest concern in D+/R- heart transplant recipients, highlighting the need for targeted prophylaxis in this population.<sup>160–162</sup>

### **Perioperative infection prophylaxis and treatment in pediatric heart transplant recipients**

Risk factors for invasive fungal infections in the pediatric population include pretransplant ECMO and early invasive procedures, and these infections have been associated with significant morbidity and mortality. Intravenous antifungal prophylaxis should be considered for infants (<1 year of age) with an open chest and/or requiring ECMO support in the perioperative period. Most cases of PJP among pediatric heart transplant recipients occur within the first 2 years of

transplant. Prophylaxis for *Pneumocystis jiroveci* should be instituted for a minimum 3 months up to 24 months after HT.<sup>163–167</sup>

### **Management of Fontan patients**

The number of palliated single ventricle patients continues to grow with 30-year survival is estimated 85% after Fontan surgery.<sup>168</sup> Failing Fontan physiology, secondary to ventricular dysfunction or failure with preserved function are indications for transplantation that may affect 2 to 4% of long-term survivors at 20 years of surgery.<sup>168–170</sup> Survival after listing and transplantation has greatly improved, but previous Fontan surgery is recognized as a significant risk factor for a poor outcome after transplantation both in children and adults. There are no clear criteria for timing of transplant. However, delay in referral for evaluation may limit heart transplantation due to progression of Fontan associated liver disease. In this situation a combined heart-liver transplantation has been indicated with good results at experienced centers.<sup>169–173</sup>

Perioperative management of Fontan patients after heart transplantation involves comprehensive knowledge of Fontan physiology and co-morbidities. Early recognition of potential complications and pre-emptive measures are important to decrease the risk of post-transplant mortality. Vasoplegia and right ventricular failure are common complications. Methylene blue has been described for severe cases of vasoplegia. Right ventricular dysfunction in high-risk patients can be managed by inhaled nitric oxide while weaning cardiopulmonary bypass. Protein losing enteropathy (PLE) and plastic bronchitis (PB) can be expected in the early postoperative period and patients need continuation of therapy until resolution.<sup>170–174</sup> Supportive therapy for PLE and PB are patient tailored but range from improving cardiac hemodynamics with diuretics, pulmonary vasodilators and/or surgical Fontan fenestration together with correction of protein hemostasis through nutritional support and anti-inflammatory treatment with CS.<sup>172</sup>

The significance and optimal treatment of systemic-to-pulmonary arterial collateral (SPC) vessels in single ventricle patients are poorly understood. Development of such vessels is due to high venous pressure. Embolization is usually performed before Fontan completion but there is risk of formation of new collateral vessels. It has also been considered that the presence of aortopulmonary collaterals may cause high output situations in the early postoperative period after transplantation. There is data to support that pre transplant or post-transplant embolization of aortopulmonary collaterals may be beneficial for these patients.<sup>170, 172, 174, 175</sup>



## Topic 4: Early Postoperative Care of the Heart Transplant Recipient

## 2010 Prior Guideline Recommendation

Perioperative 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.

Class I, Level of Evidence C

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.

Class I, Level of Evidence C

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

Class II, Level of Evidence C

Pericardial effusions occurring after HT should be monitored by echocardiogram.

Class I, Level of Evidence C

Percutaneous or surgical drainage should be done when the pericardial effusion causes hemodynamic compromise.

Class I, Level of Evidence C

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

Class IIa, Level of Evidence C

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.

Class I, Level of Evidence C

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

Class I, Level of Evidence C

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

Class I, Level of Evidence C

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

Class I, Level of Evidence B

### New Recommendation

## 2023 Update Guideline Recommendation

It is advised that perioperative monitoring of heart transplant recipients include (1) continuous ECG monitoring; (2) postoperative 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) intermittent measurement of systemic vascular resistance; (8) continuous measurement of arterial oxygen saturation; (9) intermittent measurement of mixed venous saturation; (10) intraoperative transesophageal echocardiogram (TEE); (11) continuous assessment of urinary output.

**Class I, Level of Evidence C**

Continuing approval without change

De Vega or Ring annuloplasty can be considered for intraoperative TV regurgitation that is moderate or severe to maintain the normal size of the TV annulus.

**Class IIa, Level of Evidence C**

Continuing approval without change

Continuing approval without change

Continuing approval without change

Continuous infusion of an inotropic agent or a combination of inotropic agents 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.

**Class I, Level of Evidence C**

The following therapies are suggested: (a) isoproterenol, 1 to 10  $\mu\text{g}/\text{min}$ , or (b) dobutamine, 1 to 10  $\mu\text{g}/\text{kg}/\text{min}$   $\pm$  dopamine 1 to 10  $\mu\text{g}/\text{kg}/\text{min}$ , or (c) isoproterenol, 1 to 10  $\mu\text{g}/\text{min}$   $\pm$  dopamine 1 to 10  $\mu\text{g}/\text{kg}/\text{min}$ , or (d) milrinone, 0.375 to 0.75  $\mu\text{g}/\text{kg}/\text{min}$ , or (e) milrinone, 0.375 to 0.75  $\mu\text{g}/\text{kg}/\text{min}$   $\pm$  epinephrine 0.01 to 0.1  $\mu\text{g}/\text{kg}/\text{min}$ .

**Class I, Level of Evidence C**

Continuing approval without change

Continuing approval without change

Norepinephrine is considered the first-line agent for treatment of vasoplegia, followed by vasopressin. Other routine vasoactive

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## Topic 4: Early Postoperative Care of the Heart Transplant Recipient

2010 Prior Guideline Recommendation	2023 Update Guideline Recommendation
<b>New Recommendation</b>	medications include epinephrine, norepinephrine, dopamine, and angiotensin II. The additional use of a single dose of methylene blue may also be considered. <b>Class I, Level of Evidence C</b>
Inotropic agents that can be used to augment right ventricle (RV) function include isoproterenol, milrinone, enoximone, dobutamine, and epinephrine. Class I, Level of Evidence C	Inhaled pulmonary vasodilators that have minimal effect on systemic arterial pressure, such as nitric oxide or prostacyclin analogues (i.e., epoprostenol), should be considered in the management of RV dysfunction ± pulmonary hypertension. <b>Class I, Level of Evidence B</b>
Systemic vasodilators with pulmonary vasodilating properties, including nitroglycerine and sodium nitroprusside, can be used in the absence of systemic hypotension. Class IIa, Level of Evidence C	Continuing approval without change
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. Class IIa, Level of Evidence C	Continuing approval without change
<b>New Recommendation</b>	The relative efficacy of inhaled epoprostenol appears to be similar to that of inhaled nitric oxide and its use may be associated with significant cost savings. <b>Class IIa, Level of Evidence B</b>
<b>New Recommendation</b>	MCS, principally involving VA-ECMO, is an effective management strategy for severe primary graft dysfunction (PGD). Other forms of MCS, such as LVAD, RVAD, and BiVAD may also be considered in select cases. <b>Class I, Level of Evidence B</b>
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. Class I, Level of Evidence B	Continuing approval without change
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. Class I, Level of Evidence B	Continuing approval without change
Support for either LV or RV failure should escalate from pharmacotherapy to IABP to MCS. Class I, Level of Evidence B	Continuing approval without change
Small ventricular assist devices (VADs) such as the TandemHeart and LevitronixCentrimag can provide adequate support for RV, LV, or biventricular (BiV) failure, and have benefits of ease of implantation, management, and explant. Class I, Level of Evidence C	Short-term MCS can provide adequate support for RV, LV, or biventricular (BiV) failure, and have benefits of ease of implantation, management, and explant. <b>Class I, Level of Evidence C</b>
In the presence of hemodynamic instability, cardiac tamponade should be excluded by direct surgical exploration. The presence	Continuing approval without change

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## Topic 4: Early Postoperative Care of the Heart Transplant Recipient

2010 Prior Guideline Recommendation	2023 Update Guideline Recommendation
of hyperacute/antibody-mediated rejection should also be excluded. If hemodynamic instability persists in the absence of cardiac tamponade, MCS should be considered. Class IIa, Level of Evidence C	
The timing of 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. Class IIa, Level of Evidence C	Continuing approval without change
Use of ECMO support in adults requires consideration of the risk of infection, immobility, and need for anticoagulation. Class IIb, Level of Evidence C	Continuing approval without change
The increased risk of postoperative 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. Class IIb, Level of Evidence C	Continuing approval without change
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 IIb, Level of Evidence C	Continuing approval without change
Pharmacologic chronotropic agents, including isoproterenol and theophylline can be used in the perioperative setting to increase heart rate. Class I, Level of Evidence B	Pharmacologic chronotropic agents, including isoproterenol, theophylline, terbutaline, and albuterol can be used in the perioperative setting to increase heart rate. <b>Class I, Level of Evidence B</b>
Atrial and ventricular temporary epicardial pacing wires should be placed at the time of HT even if the initial rhythm is sinus. Class I, Level of Evidence B	Continuing approval without change
After HT, temporary pacing should be initiated in the setting of relative bradycardia to maintain heart rates of > 90 beats/min. Class I, Level of Evidence B	Continuing approval without change
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.	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 (AAAIR) or dual-paced, dual-sensed, dual-response to sensing, rate modulation (DDDR) pacemakers with minimized ventricular pacing are preferable. <b>Class I, Level of Evidence C</b>
Treatment of tachyarrhythmias should be aimed at rate control. Class I, Level of Evidence B	Continuing approval without change
Persistent tachyarrhythmias, whether atrial or ventricular, should prompt investigation of possible rejection and electrophysiological evaluation if rejection is absent. Class I, Level of Evidence B	Continuing approval without change
Sustained ventricular tachycardia (SVT) should be evaluated with both an angiogram and an endomyocardial biopsy (EMB). Class I, Level of Evidence B	Continuing approval without change
The Class III anti-arrhythmics sotalol and amiodarone can be safely used in HT recipients and have minimal interaction with	Continuing approval without change

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## Topic 4: Early Postoperative Care of the Heart Transplant Recipient

2010 Prior Guideline Recommendation	2023 Update Guideline Recommendation
immunosuppressive agents. Class IIa, Level of Evidence C Non-dihydropyridine calcium channel blockers (CCBs) and $\beta$ -blockers may be used in HT recipients for rate control. Class IIa, Level of Evidence B	Continuing approval without change
<b>New Recommendation</b>	Adenosine use may be considered in HT recipients with supraventricular tachyarrhythmias if they are closely monitored and low doses are administered (25 mcg/kg; 1.5 mg if $\geq$ 60 kg). <b>Class IIb, Level of Evidence C</b>
<b>New Recommendation</b>	Removal of pacemakers and associated leads should ideally be considered at the time of HT. The removal of any leads retained postoperatively, which are known to increase the prevalence of venous thrombosis and confer MRI contraindications, should be managed with multidisciplinary assessment. <b>Class IIa, Level of Evidence C</b>
The CVP should be maintained between 5 and 12 mm Hg, a level that provides adequate cardiac filling pressures without causing RV overload. Class I, Level of Evidence C	Continuing approval without change
Colloid replacement is generally preferred in the first 24 hours after HT; blood, if indicated, is the first choice. Class I, Level of Evidence C	Continuing approval without change
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. Class I, Level of Evidence B	Continuing approval without change
Blood products should be leukocyte-depleted. Blood products should be cytomegalovirus (CMV) negative if donor and recipient are CMV negative. Class I, Level of Evidence B	Continuing approval without change
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. Class I, Level of Evidence B	Continuing approval without change
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. Class I, Level of Evidence B	Continuing approval without change
Ultrafiltration should be considered if RAP remains elevated (> 20 mm Hg) despite pharmacologic interventions. Class IIa, Level of Evidence B	Continuing approval without change
Delay of initiation of calcineurin inhibitor (CNI) therapy should be considered if there is significant preoperative renal insufficiency or deterioration of kidney function in the first 2 postoperative days. Class IIb, Level of Evidence C	Continuing approval without change
Oral hypoglycemic agents should be discontinued preoperatively. Class I, Level of Evidence C	Continuing approval without change
A continuous infusion insulin regimen should be used to maintain blood glucose below 200 mg/dL during the intensive care unit (ICU) stay.	A continuous infusion insulin regimen is reasonable to maintain blood glucose between 140 and 180 mg/dL starting during surgery and maintained during the intensive care unit (ICU) stay. <b>Class IIa, Level of Evidence B</b>

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## Topic 4: Early Postoperative Care of the Heart Transplant Recipient

2010 Prior Guideline Recommendation	2023 Update Guideline Recommendation
<b>New Recommendation</b>	Non-diabetic recipients can benefit from more strict glucose control (target <140 mg/dL). <b>Class IIa, Level of Evidence B</b>
Aggressive management of hyperglycemia should be continued for the duration of hospitalization. Class IIa, Level of Evidence C	Continuing approval without change
Pre-operative antibiotic prophylaxis should be used before the transplant operation. Class I, Level of Evidence B	Continuing approval without change
Drugs should be selected based upon their activity against usual skin flora, specifically <i>Staphylococcus</i> species. Class I, Level of Evidence B	Perioperative antimicrobials should be selected based upon their activity against skin flora, including <i>Staphylococcus</i> species. <b>Class I, Level of Evidence B</b>
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.	If a chronically infected device such as a VAD, ECMO circuit, or a pacemaker is present, perioperative antimicrobials should be selected based upon microbiologic sensitivities, and the duration of therapy should be dependent upon the extent of infection. <b>Class I, Level of Evidence B</b>
In the event that the donor had an ongoing bacterial infection, a course of suitable anti-biotics should be considered. Class I, Level of Evidence B	Continuing approval without change
<b>New Recommendation</b>	In the absence of disseminated infection, heart transplants performed using bacteremic donors should receive antibiotics targeted to the organism isolated from the donor in consultation with Transplant Infectious Diseases. <b>Class I, Level of Evidence C</b>
<b>New Recommendation</b>	A longer course of therapy is recommended in the setting of disseminated infection, including endocarditis, in consultation with Transplant Infectious Diseases. <b>Class I, Level of Evidence C</b>
<b>New Recommendation</b>	The efficacy of antimicrobial prophylaxis for individuals requiring MCS for primary graft dysfunction is unknown. In this situation, consultation with Transplant Infectious Diseases is recommended, and the choice and duration of antimicrobials should be dependent upon individual clinical risk factors. <b>Class IIb, Level of Evidence C</b>
Prophylaxis against CMV should be initiated within 24 to 48 hours after HT.	The initiation of intravenous ganciclovir or oral valganciclovir within 10 days of HT is recommended for antiviral prophylaxis in D+/R- and R+ recipients when utilizing a universal prophylaxis strategy. The recommended duration of prophylaxis is 3-6 months for D+/R- and 3 months for R+. <b>Class I, Level of Evidence A</b>
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.	The CMV serologic status of the donor and recipient should be used to stratify the recipient as low-risk, intermediate-risk, or high-risk for developing CMV infection. <b>Class I, Level of Evidence A</b>
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.	Prophylaxis with acyclovir, valacyclovir, or famciclovir should be considered for heart transplant recipients who are CMV -/-, seropositive for HSV-1 and/or HSV-2, and who are not receiving CMV prophylaxis with an HSV-active agent. <b>Class I, Level of Evidence B</b>

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## Topic 4: Early Postoperative Care of the Heart Transplant Recipient

## 2010 Prior Guideline Recommendation

**New Recommendation****New Recommendation**

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).

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 via the hepatic cytochrome P-450 system (CYP3A). (3) Atovaquone (1,500 mg PO QD). (4) Clindamycin and pyrimethamine.

Class I, Level of Evidence B

**New Recommendation**

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

Class IIb, Level of Evidence C

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

Class IIb, Level of Evidence C

## 2023 Update Guideline Recommendation

Antiviral prophylaxis is recommended over pre-emptive therapy for recipients at high-risk for CMV infection (D+/R-).

**Class IIa, Level of Evidence C**

There is insufficient evidence to support the use of antiviral prophylaxis for post-transplant lymphoproliferative disorder prevention in EBV-mismatched (D+/R-) heart transplant recipients. Pre-emptive EBV viral load monitoring should be considered in this setting.

**Class IIa, Level of Evidence C**

There is insufficient evidence to support universal prophylaxis against *Candida* spp. following heart transplantation.

**Class IIa, Level of Evidence C**

The preferred agent for prophylaxis against *Pneumocystis jiroveci* is trimethoprim-sulfamethoxazole. **Class I, Level of Evidence A** Alternate prophylactic regimens for *Pneumocystis jiroveci* in those intolerant of trimethoprim-sulfamethoxazole include, dapsone, atovaquone, clindamycin, pyrimethamine and inhaled pentamidine.

**Class I, Level of Evidence B**

Regardless of pre-transplant serostatus, heart transplant recipients residing in areas endemic for *Coccidioides* should receive 6-12 months of prophylaxis with an oral azole. There is insufficient evidence to support universal or targeted testing for *Coccidioides* among deceased donors. However, heart transplant recipients who receive organs from donors with prior or active coccidiomycosis should be treated with 6-12 months of pre-emptive fluconazole followed by either lifelong step-down therapy or serologic and clinical monitoring.

**Class I, Level of Evidence C**

Continuing approval without change

Prophylaxis against *Pneumocystis jiroveci* is recommended for at least 6-12 months following heart transplant.

**Class I, Level of Evidence B**

## Topic 5: Evaluation of allosensitization, approaches to sensitized heart transplant recipients, and hyperacute and delayed antibody-mediated rejection

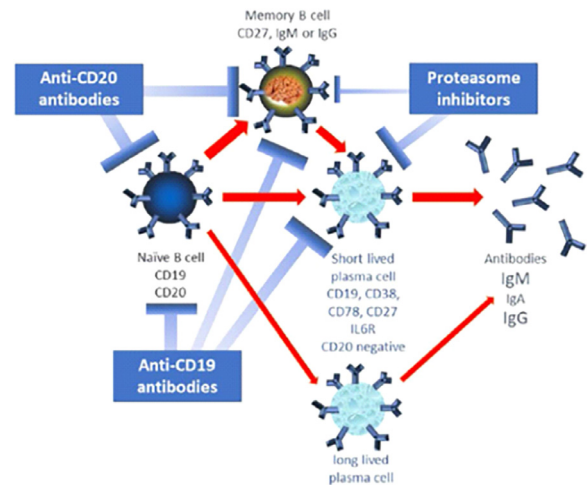
### Risk-assessment and prophylaxis strategies for allosensitized heart transplant candidates

Antibody mediated rejection has an important prognostic impact after heart transplantation. Antibody monitoring and management strategies before and after heart transplant have evolved in recent years leading to development of consensus statements from various societies.<sup>176–178</sup>

**Antibody testing and the virtual crossmatch.** HLA antibody testing is important to detect potentially harmful antibodies. Failure to recognize unacceptable antigens can be deleterious. However, identifying clinically irrelevant antibodies and avoiding corresponding antigens unnecessarily restricts organ access. Most transplant programs now utilize highly sensitive solid phase assays for antibody screening. Single antigen bead assays have enabled virtual crossmatching by removing the need for a prospective physical crossmatch at transplant and expanding the geographic procurement area. Patients at risk for suboptimal outcome post-transplant are defined as having a PRA >10% or with donor-directed antibodies at the time of transplantation.

Antibody mean fluorescent intensity (MFI) is commonly used to assess strength of sensitization and to predict a positive crossmatch. MFI represents a measure of antibody-antigen binding or HLA molecule bead saturation rather than a direct measure of antibody titer and is therefore affected by several technical and biologic factors.<sup>179</sup> Relevant levels of MFI are therefore specific to laboratories and there is no standardization or established thresholds internationally. The presence of endogenous interfering molecules can also mask detection of HLA antibodies. Referred to as the prozone effect, these substances may be diluted out, inactivated, or denatured by heat inactivation, adding dithiothreitol or ethylenediaminetetraacetic acid. The C1q assay identifies antibodies capable of fixing complement. C1q binding DSA strongly correlate with a positive cytotoxic crossmatch and are also associated with the development of early antibody mediated rejection (AMR) post heart-transplant.<sup>180</sup> These assays may be used in combination to risk stratify highly sensitized patients for donor compatibility through identification of potentially cytotoxic antibodies.<sup>181</sup> The calculated panel reactive antibody (cPRA) provides an estimation of the compatible donor pool by determining the population frequency of antigens to be avoided due to presence of corresponding cytotoxic antibodies. Although a virtual crossmatch allows expansion of the donor pool, antibodies to shared epitopes may still confer some risk. High resolution HLA genotyping and retrospective crossmatching helps mitigate this risk.

Non-HLA antibodies can also play a role in antibody mediated rejection, and, if possible, could be considered in the assessment of AMR.<sup>176</sup> Serological presence of



**Figure 1** Established effects of some targeted interventions. Blue bars symbolize depleting or reducing effect. Anti-CD20 antibodies show strong effect on naïve, effector, and memory B cells but no effect on plasma cells, which are not expressing CD20. Proteasome inhibitors show strong effect on PC and moderate effect on memory B cells. Anti-CD19 cells target PC but are currently not available as an effective clinical therapeutic for transplant. Effect of all of these therapies on LLPC is unclear but appears to be limited. (IL: interleukin, LLPC: long lives plasma cell, PC: plasma cell). Transplantation 103(5):p 890–898, May 2019.

antibodies is a dynamic phenomenon. Therefore, periodic monitoring is advised especially after a sensitizing event or in patients on desensitization therapies awaiting heart transplantation.

In children the use of a human vascular homograft for reconstruction of congenitally hypoplastic great vessels was found to be a key contributor to HLA sensitization but can be prevented by decellularization of the homografts for example, with glutaraldehyde.<sup>182–185</sup> As in adults, in pediatric allosensitized transplant candidates, prospective serological crossmatch or virtual crossmatch should be done to ascertain donor immunocompatibility. In children or adults with congenital heart disease associated protein losing enteropathy immunoglobulins are lost via the intestine including HLA antibodies, quantification of plasma IgG, and recurrent HLA testing help reducing the risk of missing sensitization.

**Desensitization strategies.** Desensitization therapies typically target critical components of the humoral response, including antibodies, B cells, plasma cells and complement activation (Table 9 and Figure 1). Efficacy is highly variable and there have been no randomized trials of desensitization to assess efficacy. Even with successful depletion of antibody, the risk of a memory response may potentially persist. Perioperative plasmapheresis and IV immunoglobulin or eculizumab at transplant may be considered in highly sensitized patients, with eculizumab being associated with a lower risk for AMR.<sup>186</sup>

The 2009 ISHLT Consensus on antibody monitoring provided some direction on frequency of antibody testing.<sup>178</sup> For nonsensitized patients awaiting heart transplant, HLA antibody screens may be obtained every 6 months. For sensitized patients, these are recommended every 3 months.

Patients on MCS should have HLA antibodies checked every 3 months. After blood transfusions and infections, HLA antibodies should be checked 1 to 2 weeks after the event. When using a desensitization, strategy, HLA antibodies should be checked 1 to 2 weeks after therapy.

After transplant, routine surveillance for antibody mediated rejection is recommended, with attention to

pathological and immunopathological findings in the endomyocardial biopsy. Antibody mediated rejection diagnosis is based on pathology of allograft biopsies, but post-transplant circulating antibody monitoring is also recommended, with particular attention to de-novo donor-specific antibodies, considering their association with poor patient survival.

Topic 5: Evaluation of Allosensitization, Approaches to Sensitized Heart Transplant Recipients, and Hyperacute and Delayed Antibody-Mediated Rejection

2010 Prior Guideline Recommendation

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

Class I, Level of Evidence C

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.

Class I, Level of Evidence C

The anti-HLA class I and II specificities (i.e., 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.

Class I, Level of Evidence C

**New Recommendation**

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.

Class I, Level of Evidence C

The complement fixation capability of detected antibodies should be reported.

Class I, Level of Evidence C

**New Recommendation**

**New Recommendation**

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. Class IIa, Level of Evidence C

2023 Update Guideline Recommendation

Continuing approval without change

Continuing approval without change

The anti-HLA class I and II specificities (i.e., 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 antibody threshold for unacceptable rejection risk. A mean fluorescence intensity (MFI) less than 5,000 is generally considered to be an acceptable threshold.

**Class I, Level of Evidence C**

It is recommended that calculated PRA (c-PRA) based on recipient antibody specificity and population antigenemic prevalence be determined and reported to aid in matching.

**Class I, Level of Evidence C**

Continuing approval without change

The complement fixation capability of detected antibodies may be beneficial as it may identify more clinically relevant antibodies. This can be assessed through specific complement-fixing assays or sera dilution (higher antibody titers are associated with higher likelihood of complement fixing capacities).

**Class IIa, Level of Evidence C**

If known, presence of non-HLA antibodies, such as major histocompatibility complex (MHC) Class I polypeptide-related sequence A (MICA) or angiotensin II type 1 receptor-activating antibodies (AT1R), antibodies to self-antigens are reasonable to report and consider when assessing AMR risk.

**Class IIa, Level of Evidence C**

Prospective or Virtual crossmatch should be performed in recipients with PRA  $> 10\%$ .

**Class I, Level of Evidence C**

Continuing approval without change



*(Continued)***Topic 5: Evaluation of Allosensitization, Approaches to Sensitized Heart Transplant Recipients, and Hyperacute and Delayed Antibody-Mediated Rejection**

2010 Prior Guideline Recommendation	2023 Update Guideline Recommendation
<p>A PRA <math>\geq</math> 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. Class IIa, Level of Evidence C</p>	<p>A PRA <math>&gt;</math> 10% indicates allosensitization, however, many centers use cPRA<math>&gt;</math>50% as a threshold for desensitization. Therapies aimed at reducing allosensitization may be considered in selected patients to minimize the need for a prospective donor/recipient crossmatch. <b>Class IIa, Level of Evidence C</b></p>
<p>The results of the retrospective donor recipient crossmatch may be considered to make decisions regarding immunosuppressive therapy. Class IIa, Level of Evidence C</p>	<p>Continuing approval without change</p>
<p>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. Class IIb, Level of Evidence C</p>	<p>Continuing approval without change</p>
<p>Choices to consider as desensitization therapies include IV immunoglobulin (Ig) infusion, plasmapheresis, either alone or combined, rituximab, and in very selected cases, splenectomy. Class IIb, Level of Evidence C</p>	<p>Continuing approval without change</p>
<p>A large randomized controlled clinical trial is needed to assess the effectiveness of desensitization strategies and their impact on outcomes after HT. Class IIb, Level of Evidence C</p>	<p>Continuing approval without change</p>
<p>The presence of anti-HLA antibodies should be regularly monitored in allosensitized patients undergoing desensitizing therapies until a compatible heart allograft becomes available. Class IIa, Level of Evidence C</p>	<p>Continuing approval without change</p>
<p><b>New Recommendation</b></p>	<p>In patients awaiting transplant, the presence of anti-HLA antibodies can be reassessed 1 to 2 weeks following a sensitizing event to reduce the possibility of positive cross match. <b>Class IIa, Level of Evidence C</b></p>
<p><b>New Recommendation</b></p>	<p>In allosensitized candidates, including those undergoing desensitizing therapies, it is reasonable to monitor anti-HLA antibodies at regular intervals according to their urgency status until a compatible heart allograft becomes available to reduce the possibility of a positive crossmatch to facilitate matching. <b>Class IIa, Level of Evidence C</b></p>
<p><b>New Recommendation</b></p>	<p>It is reasonable to measure donor-specific antibodies (DSA) levels when antibody-mediated rejection (AMR) is suspected or confirmed by endomyocardial biopsy (EMB). <b>Class IIa, Level of Evidence C</b></p>
<p>In ambulatory, non-sensitized HT candidates it is reasonable to measure anti-HLA antibodies every 6 months. Class IIb, Level of Evidence C</p>	<p>In ambulatory, non-sensitized HT candidates it may be reasonable to measure anti-HLA antibodies every 6 months. <b>Class IIb, Level of Evidence C</b></p>
<p>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. Class IIb, Level of Evidence C</p>	<p>In HT candidates requiring blood transfusions, anti-HLA antibodies determination should be repeated 1 to 2 weeks later and prospective donor/recipient crossmatch is required in the interim period if a suitable donor organ becomes available. <b>Class IIb, Level of Evidence C</b></p>
	<p>Continuing approval without change</p>

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**Topic 5: Evaluation of Allosensitization, Approaches to Sensitized Heart Transplant Recipients, and Hyperacute and Delayed Antibody-Mediated Rejection**


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**2010 Prior Guideline Recommendation****2023 Update Guideline Recommendation**

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

Class IIb, Level of Evidence C

Circulating immunoglobulins should be measured before and after plasmapheresis or immunoabsorption. Class IIb, Level of Evidence C

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

Class IIb, Level of Evidence C

**New Recommendation****New Recommendation****New Recommendation**

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. Class IIb, Level of Evidence C

Initial therapy of AMR can include immunoabsorption and corticosteroid (CS) or plasmapheresis/low dose of IV Ig and CS. Class IIa, Level of Evidence C

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

Class IIa, Level of Evidence C

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

Class IIa, Level of Evidence C

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.

Class IIb, Level of Evidence C

**New Recommendation**

Measuring circulating immunoglobulins before and after plasmapheresis or immunoabsorption may be useful to monitor response to therapy.

**Class IIb, Level of Evidence C**

Measuring lymphocyte subpopulations before and after the use of rituximab may be useful in guiding therapy.

**Class IIb, Level of Evidence C**

Biopsy samples obtained for surveillance of rejection should be assessed for both cellular and antibody-mediated rejection.

**Class I, Level of Evidence C**

Diagnosis of AMR should be based on immunopathologic findings using ISHLT pathologic grading criteria, in addition to clinical findings.

**Class I, Level of Evidence C**

The presence of DSAs supports the diagnosis of AMR and can be useful in monitoring response to treatment.

**Class IIa, Level of Evidence C**

Continuing approval without change

Initial therapy of AMR can include immunoabsorption, plasmapheresis, high dose corticosteroid (CS), antilymphocyte antibodies, and/or IV Ig.

**Class IIa, Level of Evidence C**

Rituximab, bortezomib, and anticomplement antibodies can be considered as secondary therapy for AMR.

**Class IIa, Level of Evidence C**

Continuing approval without change

Continuing approval without change

Consideration may be given to treat rising DSA in the early post-transplant period as they may represent a rapid amnesic antibody response. Persistent and de novo DSA are associated with poor patient survival.

**Class IIb, Level of Evidence C**

## Topic 6: Management of ABO "Incompatible" heart transplant recipients

### Management of ABO "Incompatible" heart transplant recipients

ABO incompatible (ABOi) heart transplantation has evolved from an experimental approach<sup>187, 188</sup> to evidenced clinical practice that is routinely considered for the majority of patients listed for transplantation that are under 2 years of age<sup>189, 190</sup> but has also been performed in older children in UK and Canada based on isohemagglutinins. Expected outcomes and graft survival for infant heart recipients are comparable to ABO compatible (ABOc) transplantation. ABOi listing reduces waiting list time especially for blood group O recipients. Additionally, this approach has reduced waitlist mortality.<sup>187, 190</sup> Recently published multi-center experience<sup>191</sup> in the last 20 years confirms ABOi as a clinically safe approach with similar outcomes to ABOc in respect of survival, incidence of rejection, CAV and malignancy that had been published previously.<sup>190</sup> Immunologic immaturity and absence of production of A and B isohemagglutinins (IH) by infants offers a window of

opportunity for this therapy. Dilution hemagglutination testis the standard method to detect and quantify A/B antibodies<sup>192–194</sup> but exact data is limited due to laboratory variability.<sup>195</sup> Initially, ABOi heart transplants were performed if IH levels were  $\leq 1:4$ .<sup>189</sup> Recent data suggests that ABOi heart transplantation has been performed successfully with higher isohemagglutinin titers at experienced centers.<sup>187, 190, 196</sup> Plasma exchange<sup>188</sup> is the current method to clear isohemagglutinins. Plasma exchange is not necessary at the time of surgery if IH levels are  $< 1:4$ , however, needs to be undertaken if levels are  $> 1:8$ . Recently, centers have reported on expanding use of ABOi transplant to older children or those with higher IH levels.<sup>189</sup> Retrospective analysis demonstrated acceptable outcomes with an increased risk of AMR suggesting potential need for immunosuppression modification (i.e., Anti-thymocyte globulin [ATG] as induction therapy for high-risk patients; treatment with rituximab pre-transplant or post-transplant in case of increasing IH titers). Intraoperative immunoadsorption has also been described as a new novel method for antibody clearing that has been addressed as useful to avoid the exposure to large amounts of fluid needed for standard plasma exchange.<sup>196–199</sup>

Topic 6: Management of ABO "Incompatible" Heart Transplant Recipients	
2010 Prior Guideline Recommendation	2023 Update Guideline Recommendation
The upper limit of age or isohemagglutinin titer for ABO-incompatible pediatric HT remains unclear. Class IIa, Level of Evidence C <b>New Recommendation</b>	Continuing approval without change  ABO-incompatible transplant in children less than 2 years of age with low levels of isohemagglutinin can be performed with comparable outcome to recipients of ABO compatible organs. <b>Class IIa, Level of Evidence B</b>
ABO-incompatible HT can be safely performed in the pediatric population in the presence of positive isohemagglutinin titers against the donor organ. Class IIa, Level of Evidence C <b>New Recommendation</b>	Continuing approval without change  ABO-incompatible HT can be performed in children with low titers but the upper limit of age or isohemagglutinin titer for ABO-incompatible pediatric HT remains unclear. <b>Class IIa, Level of Evidence C</b>
ABO-incompatible HT, especially in the presence of donor-specific isohemagglutinins $> 1:4$ , should be performed in an experienced center. Class IIa, Level of Evidence C ABO-incompatible HT can be undertaken by performing plasma exchange using the CPB circuit to remove donor specific isohemagglutinins. Class IIa, Level of Evidence C <b>New Recommendation</b>	Continuing approval without change  Continuing approval without change
Plasma exchange using the CPB circuit allows the safe transplantation of ABO-incompatible organs without the need of aggressive pre-operative immunosuppressive	Isohemagglutinin (IH) levels should be measured and negative before aortic cross clamp removal. Otherwise, it is reasonable to consider further plasma exchange. <b>Class I, Level of Evidence C</b>  Continue approval without change

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## Topic 6: Management of ABO "Incompatible" Heart Transplant Recipients

## 2010 Prior Guideline Recommendation

## 2023 Update Guideline Recommendation

therapies or splenectomy.  
Class IIa, Level of Evidence C

**New Recommendation**

Patients with isohemagglutinin titers <1:4 may not need plasma exchange at the time of transplantation.

**Class IIa, Level of Evidence B****New Recommendation**

It is reasonable for patients with isohemagglutinin titers >1:8 to undergo removal of antibodies with plasma exchange using the CPB circuit at the time of surgery.

**Class IIa, Level of Evidence C**

Serial measurements of isohemagglutinin titers should be done in the postoperative 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.

Class IIa, Level of Evidence C

**New Recommendation**

Continuing approval without change

Standard hemagglutination methods can be used to determine serum anti-A and anti-B antibody levels at time of listing for transplant and repeated at regular intervals until transplantation.

**Class IIa, Level of Evidence B****New Recommendation**

When titers are >1:16, ABO-incompatible HT can be undertaken by performing plasma exchange using the CPB circuit to remove donor specific IH. Modification of immunosuppression is also reasonable.

**Class IIa, Level of Evidence B****New Recommendation**

Standard IH levels may have differences among different laboratories so repeated lab tests should be performed and confirmed at the time of surgery.

**Class IIa, Level of Evidence C****New Recommendation**

After transplantation IH levels should be performed at least daily in the immediate perioperative period and at increasing intervals in the follow-up period and at times of suspected rejection.

**Class IIa, Level of Evidence C**

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.

Class IIa, Level of Evidence C

Continuing approval without change

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. Class IIa, Level of Evidence C

Continuing approval without change

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.

Continuing approval without change

Class IIa, Level of Evidence C

Continuing approval without change

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*(Continued)***Topic 6: Management of ABO “Incompatible” Heart Transplant Recipients****2010 Prior Guideline Recommendation**

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.

Class IIa, Level of Evidence B

Immunosuppression management beyond the peri-operative period is similar to that of the ABO-compatible pediatric HT population.

Class IIa, Level of Evidence B

**New Recommendation****New Recommendation**

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

Class I, Level of Evidence C

**2023 Update Guideline Recommendation**

Continuing approval without change

Induction therapy with anti-thymocyte globulin (ATG) is reasonable for patients with IH titers >1:8 or other risk factors.

**Class IIa, Level of Evidence C**

Rituximab is reasonable preoperatively if IH titers > 1:32 or added post operatively in case of increasing IH levels.

**Class IIa, Level of Evidence C**

Continuing approval without change

**Topic 7: Coagulopathies in heart transplant surgery**

Multiple areas of perioperative heart transplant coagulopathy remain without definitive randomized trials. Transfusion strategies are not well studied with varied expert guidance on appropriate clinical scenarios for transfusion.<sup>200–216</sup>

Four-factor PCCs continue to be recommended before considering recombinant factor VIIa when managing hemorrhage in cardiac surgery, however, transplant specific data are lacking. Optimal strategies for antiplatelet management and testing in patients with ischemic disease awaiting transplant requires further study. Platelet function testing appears to have limited utility before HT. Minimal data exist to

guide the use of oral P2Y12 inhibitor therapy in patients listed for transplant. Few studies have been performed specifically in HT patients with recommendations in this population largely extrapolated from evidence regarding hemostasis in general cardiac surgery.<sup>217</sup> Regarding patients with a history of heparin-induced thrombocytopenia, retesting for IgG heparin/platelet factor four antibodies is recommended before HT. Cardiac surgery- and HT-specific data suggest heparin is safe to use during CPB in patients who are negative for antibodies before transplant, with close platelet monitoring in the postoperative period. Patients with positive antibodies before HT should receive a non-heparin anticoagulant during CPB and postoperatively, as needed.

**Topic 7: Coagulopathies in Heart Transplant Surgery****2010 Prior Guideline Recommendation**

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

Class I, Level of Evidence C

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

Class IIa, Level of Evidence C

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.

Class I, Level of Evidence C

**2023 Update Guideline Recommendation**

An assessment of perioperative bleeding risk including history of post-traumatic or postsurgical bleeding, family history of bleeding, the use of medications that alter coagulation, and liver disease with an elevated model for end-stage liver disease (MELD)-XI score should be carefully evaluated.

**Class I, Level of Evidence C**

Continuing approval without change

Adequate anticoagulation as assessed by activated clotting time (ACT) should be obtained before initiation of cardiopulmonary bypass (CPB) and at regular intervals during HT to gauge the activity of heparin while the recipient remains on CPB.

**Class I, Level of Evidence C***(continued on next page)*

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## Topic 7: Coagulopathies in Heart Transplant Surgery

## 2010 Prior Guideline Recommendation

Thromboelastography may be useful during the HT surgery to further elucidate the status of the patient's hemostasis.  
Class IIa, Level of Evidence C

Fibrinogen levels and D-Dimer values should be measured postoperatively because these are tests of fibrinolysis and correlate with the risk of bleeding after HT surgery.  
Class IIa, Level of Evidence C

Platelet function can be measured either by platelet aggregometry or by a point of care assay such as the platelet function assay 100 (PFA-100) during the HT surgery.  
Class IIa, Level of Evidence C  
Thromboelastography may be repeated after HT surgery to monitor patients' hemostasis.  
Class IIa, Level of Evidence C

**New Recommendation**

Pre-operatively, the international normalized ratio (INR) should be reduced to  $\leq 1.5$ .  
Class IIa, Level of Evidence C  
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.  
Class I, Level of Evidence C

**New Recommendation****New Recommendation**

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.  
Class I, Level of Evidence C  
The absence of platelet factor 4/heparin antibodies should be confirmed.  
Class IIa, Level of Evidence C  
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.  
Class I, Level of Evidence C

## 2023 Update Guideline Recommendation

Perioperative viscoelastic tests, thromboelastography (TEG) and rotational thromboelastometry (ROTEM), may be useful in HT surgery to analyze full clot formation profiles, including platelet function, in further elucidating the recipient's anticoagulation status.  
**Class IIa, Level of Evidence C**

Postoperative measurements of fibrinogen and D-dimer values, which correlate with increased risk of bleeding after HT may be measured in recipients identified as having specific increased risks for vascular thrombosis.  
**Class IIb, Level of Evidence C**

Continuing approval without change

**Recommendation removed**

Anemia screening and management for patients listed for HT is recommended.  
**Class IIa, Level of Evidence C**

Continuing approval without change

Four-factor prothrombin complex concentrates and/or Vitamin K should be considered for INR reversal as they have been shown to be safe, effective, and reduce intraoperative blood product utilization.  
**Class IIa, Level of Evidence C**

A protocolized approach to warfarin reversal should be utilized for LVAD patients admitted for HT.  
**Class I, Level of Evidence C**

Until more evidence is available to describe the safe reversibility of direct oral anticoagulants (DOAC) before HT, warfarin should be given in preference to DOACs in patients actively listed for transplant who require systemic anticoagulation.  
**Class IIa, Level of Evidence C**

Continuing approval without change

Continuing approval without change

Continuing approval without change

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## Topic 7: Coagulopathies in Heart Transplant Surgery

## 2010 Prior Guideline Recommendation

## 2023 Update Guideline Recommendation

**New Recommendation**

Heparin use for CPB at time of transplantation is reasonable in patients with a history of heparin-induced thrombocytopenia (HIT) but who are negative for IgG antibodies against the platelet factor 4/heparin complex before HT with monitoring of platelet counts for at least 5 days post-operatively; with use of a non-heparin anticoagulant if systemic anticoagulation is required.

**Class IIa, Level of Evidence C****New Recommendation**

HIT antibody testing before transplant listing is reasonable in patients with history of HIT, and ideally at the time of admission for HT.

**Class I, Level of Evidence C****New Recommendation**

Lower doses of aspirin ( $\leq 100$  mg daily) are reasonable for recipients listed for HT with an indication for this therapy if feasible.

**Class I, Level of Evidence C**

Alternative anticoagulants can be used preoperatively and postoperatively 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.

Continuing approval without change

Class I, Level of Evidence C

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.

Continuing approval without change

Class I, Level of Evidence C

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

Continuing approval without change

Class IIa, Level of Evidence C

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.

Continuing approval without change

Class IIa, Level of Evidence C

**New Recommendation**

Point-of-care coagulation tests should be utilized to inform perioperative blood product administration.

**Class I, Level of Evidence B**

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

Continuing approval without change

Class IIa, Level of Evidence B

Recombinant factor VIIa may be used in cases of intractable or excessive bleeding with HT surgery.

Recombinant Factor VIIa may be utilized as a last-line therapy for refractory hemorrhage. Four-factor PCC, up to 50 units/kg or 5,000 units total, should be utilized ahead of rFVIIa in cases of persistent bleeding.

**Class IIb, Level of Evidence C**

Class IIb, Level of Evidence C

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

Continuing approval without change

Class III, Level of Evidence B

Desmopressin is not recommended for routine use because its modest reduction in bleeding has been associated with adverse clinical events.

Continuing approval without change

Class III, Level of Evidence A

**Topic 8: Documentation and communication with the multidisciplinary team**

Topic 8: Documentation and Communication With the Multidisciplinary Team	
2010 Prior Guideline Recommendation	2023 Update Guideline Recommendation <sup>218,219</sup>
Transplant centers must have a multidisciplinary approach to patient management. Class I, Level of Evidence C	Continuing approval without change
The HT team should have regularly scheduled meetings of all disciplines involved. Class I, Level of Evidence C	Continuing approval without change
Social work, psychology and psychiatry specialists should be integrated into the patient management team. Class IIa, Level of Evidence B	Continuing approval without change except for the addition of “psychology” to acknowledge the relevance of necessary multidisciplinary Teamwork.
Transplant centers should strive to have specialty-trained pharmacists or physicians with expertise in pharmacology as part of the multidisciplinary team. Class IIa, Level of Evidence B	Continuing approval without change
Integration of input from pharmacists and infectious disease specialists is important during the development of treatment protocols for HT recipients. Class IIb, Level of Evidence B	Continuing approval without change
Dieticians should be involved in the care of HT recipients to provide input regarding prevention of weight gain and maintenance of glucose control. Class IIb, Level of Evidence C	Continuing approval without change
<b>New Recommendation</b>	Post-transplant nurse coordinators should be involved in coordinating the care of inpatient and outpatient HT recipients. <b>Class I, Level of Evidence C</b>
<b>New Recommendation</b>	Physical therapists and occupational therapists are beneficial in the post-transplant care of HT recipients, to promote early mobilization and rehabilitation. <b>Class IIa, Level of Evidence C</b>

**Topic 9: Use of extracorporeal membrane oxygenation for the management of primary graft failure in pediatric heart transplant recipients**

Topic 9: Use of Extracorporeal Membrane Oxygenation for the Management of Primary Graft Failure in Pediatric Heart Transplant Recipients	
2010 Prior Guideline Recommendation	2023 Update Guideline Recommendation <sup>192–194,204,218,220–226</sup>
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. Class IIa, Level of Evidence C	Continuing approval without change
ECMO should be promptly instituted when progressive heart allograft dysfunction occurs post-operatively. Class IIa, Level of Evidence C	Continuing approval without change
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. Class IIa, Level of Evidence C	Continuing approval without change
Left heart distension during ECMO support should be aggressively treated because it will compromise pulmonary function and impede LV recovery. Class IIa, Level of Evidence C	Continuing approval without change

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## Topic 9: Use of Extracorporeal Membrane Oxygenation for the Management of Primary Graft Failure in Pediatric Heart Transplant Recipients

2010 Prior Guideline Recommendation	2023 Update Guideline Recommendation <sup>192–194,204,218,220–226</sup>
Clinical and echocardiographic variables should be serially assessed to determine if myocardial recovery is occurring. Class IIa, Level of Evidence C	Continuing approval without change
Objective signs of recovery should lead to weaning and discontinuation of ECMO support. Class IIa, Level of Evidence C	Continuing approval without change
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. Class IIb, Level of Evidence C	Continuing approval without change

## TASK FORCE 2: Immunosuppression and rejection

Chair: Michael Shullo

Co-Chair: Stephan Schubert

Contributing Writers: Annalisa Angelini, Lilibeth Carlos, Sonia Mirabet, Jignesh Patel, Michael Pham, Simon Urschel

### Topic 1: Rejection surveillance

#### *Mechanisms and contemporary understanding of mixed rejection*

The observed decline in cellular rejection rates over the last decade attributed to improved immunosuppression targeted at T-cell mediated injury has been accompanied by a concomitant rise in the diagnosis of antibody mediated rejection, partly due to an increased appreciation for the entity. The ISHLT Consensus has made significant progress in standardizing the pathological diagnosis of AMR (pAMR) but gaps continue to exist with regard to the understanding of extent and severity of injury.<sup>227, 228</sup> Endomyocardial measurements of specific pathogenesis-based transcripts using microarray gene analysis (Molecular Microscope<sup>®</sup>) have been shown to also accurately classify acute rejection additionally to immune-histology and better correlate with the degree of injury and disease activity.<sup>229</sup> AMR has been recognized in sensitized patients in both the early and late transplant periods and there appears to be a correlation with the development of CAV.<sup>230</sup> Failing allografts can also be preceded by detectable or non-detectable AMR for several years prior and associated with the presence of DSA, which has been shown to be associated with CAV, mortality and need for retransplantation.<sup>231</sup>

Mixed rejection, consisting of concomitant AMR with acute cellular rejection (ACR), has been described. In pediatric registry data, mixed rejection constituted 25% of rejection episodes.<sup>232</sup> In a single center study of adult heart

transplant recipients, the overall prevalence of mixed rejection was 7.8%, occurring most frequently within the first year post-transplant.<sup>233</sup> Increased severity of ACR was accompanied by AMR (but not vice versa), implicating the T-cell dependence of AMR processes. Mixed rejection in both studies was associated with significant cardiovascular mortality incremental with severity. These data support a role for the use of cytolytic therapy in the treatment of both mixed rejection and AMR.

Historically, biopsy negative rejection (BNR) was reported as a clinical entity in which the EMB did not show evidence of ACR or AMR. Many of these cases appear to be previously unrecognized AMR and in the pediatric population most BNR episodes can be empirically treated for AMR if signs of ventricular systolic or diastolic dysfunction is detectable.<sup>230, 233</sup>

#### *Indications for endomyocardial biopsy in heart transplant recipients*

*Diagnosis of acute rejection.* EMB remains the clinical gold standard for the diagnosis of acute rejection. In patients with signs or symptoms of graft dysfunction, the standard of care in adult and pediatric heart transplant (HT) recipients is to perform an EMB and histopathological evaluation of cardiac allograft tissue for evidence of ACR, AMR, or mixed rejection, along with checking the serum for donor specific antibodies and performing coronary angiogram with or without intracoronary vascular ultrasound to evaluate for cardiac allograft vasculopathy. Despite revision to the heart allograft rejection grading system in 2005, there continues to be significant interobserver variability in the determination of acute cellular rejection grades, particularly for moderate or higher severity ( $\geq 2R$ ) rejection.<sup>234</sup> More recently, the assessment of gene expression within allograft tissue and the identification of rejection-associated gene transcripts (e.g., Molecular Microscope, MMDx<sup>®</sup>) has permitted improved discrimination between T-cell mediated or antibody mediated rejection and tissue injury, but this technology may

not be clinically available outside of North America and is currently not in widespread use as a routine diagnostic test.<sup>235, 229</sup>

**Post-transplant rejection surveillance.** The majority of EMBs are performed in asymptomatic HT recipients as part of protocol-dictated routine surveillance. Contemporary data demonstrate that surveillance biopsies performed in asymptomatic patients on calcineurin-inhibitor and mycophenolate-based immunosuppressive regimens are associated with a low yield for detecting moderate or higher grade acute cellular rejection, ranging between 1 and 2%.<sup>236, 237</sup> In contrast, the yield of clinically indicated biopsies in patients with signs or symptoms of graft dysfunction was 18% in one study.<sup>238</sup> As a result, HT programs are reducing the number of routine surveillance EMB and placing greater emphasis on noninvasive rejection monitoring.

**Role of right heart catheterization.** RHC can provide an assessment of cardiac filling pressures and flows with minimal incremental risk when performed at the time of EMB. This information provides prognostic information that is complementary to histologic assessment and that can guide therapeutic interventions such as initiation of cytolytic antibody therapy or use of inotropic/vasopressor support.<sup>238</sup>

**Pediatric considerations for EMB surveillance.** While EMB has been the gold standard for detection of ACR especially in the earlier days of pediatric heart transplantation, the need for and appropriate frequency of routine surveillance EMB are controversial. Similar to adults, the frequency of ACR declines with time after transplantation however, registry data suggests that even late after transplantation, pathologically significant rejection is occasionally picked up by surveillance EMB only with no suspicion based on clinical or noninvasive monitoring, especially in children with a history of moderate to severe rejection in the early post-transplant period.<sup>239, 240</sup> Generally, ACR is less frequent in infants and children less than 5 years of age and the frequency of treated rejection in the first year post-transplant continues to decline in the present era compared to earlier eras.<sup>48</sup> Due to anatomic and size considerations in this age-group, the risk for complications of EMB is higher and the procedure always requires general anesthesia or deep sedation, thereby increasing risk and cost.<sup>241</sup> Therefore, some centers abstain from any routine surveillance EMB in children below a certain age (e.g., 1 or 2 years) or weight (e.g.,  $\leq 10$  kg). Overall center-dependent standard approaches on routine surveillance EMB show a wide variety with a first-year frequency ranging between 0 and 9 in infants and 0 to 16 in adolescents.<sup>242</sup> After the first post-HT year, surveillance EMB is also common with a high proportion of centers performing  $\geq 4$  surveillance EMB per year between years 2 to 5 and 70% performing at least annual surveillance EMB beyond 5 years after HT.<sup>243</sup> A higher frequency of EMB is reported in U.S. compared to European and other centers, and a trend toward declining EMB frequency is observed in the more recent era.<sup>242</sup> The role of echocardiographic and other noninvasive monitoring

becomes more relevant in younger patients as outlined below, since centers with high frequency EMB protocols did not have better long-term survival or earlier detection of moderate to severe cellular rejection compared to centers with low- or mid-frequency EMB.<sup>243</sup>

### **Noninvasive monitoring for acute rejection**

The diagnosis of acute cardiac allograft rejection is still challenging since rejection often occurs in asymptomatic patients and can impact the outcome of transplanted patients. EMBs remain the gold standard for monitoring rejection in the early post-transplant phase and in symptomatic patients. Since significant limitations associated with this invasive procedure have been recognized, many attempts have been carried out to identify noninvasive procedures to decrease or eliminate the use of surveillance EMBs.

**Electrophysiological parameters.** There have been no new published studies on ventricular evoked responses (VER) for the routine monitoring of acute rejection since publication of the previous guidelines. This technology has become obsolete and is no longer recommended.

**Biomarkers.** Cardiac troponins I and T are sarcomeric structural proteins that are released in the bloodstream due to cardiomyocyte injury and/or damage. Conflicting data on the use of conventional cardiac troponin I (cTnI) and T (cTnT) assays have been obtained in several studies with a lack of correlation between serum troponin levels and rejection and unacceptably high false negative results.<sup>244</sup> More promising data have been obtained with high-sensitivity troponin (hs-cTn) assays, which are 10 fold more sensitive than conventional assays. In a meta-analysis of 12 studies evaluating the use of both cTn and hs-cTn for ACR monitoring, hs-cTn assays were noted to have a greater sensitivity (82 to 100%) and negative predictive value (97 to 100%) than cTn assays for detecting ACR.<sup>244</sup> Furthermore, cTn levels, as detected by the high-sensitivity assay, were shown to increase in a graded manner with higher ACR biopsy scores.<sup>245</sup>

B-Type natriuretic peptide (BNP) is a neurohormone with various biological activities, including natriuresis, diuresis, and vasodilation, that is synthesized as a prohormone and cleaved into an active C-terminal and inactive N-terminal fragment (NT-proBNP) upon release into the circulation in response to left ventricular dysfunction. Although the association between absolute BNP and NT-ProBNP levels with ACR is weak, within-individual increases in NT-proBNP levels have been shown to be more closely related to ACR, independent of pulmonary capillary wedge pressure and left ventricular ejection fraction.<sup>246–248</sup>

### **Assessment of immunologic risk predictors**

**Gene expression profiling.** The use of peripheral blood GEP for rejection monitoring has increased since

publication of the 2010 guidelines, and transplant centers are incorporating the AlloMap<sup>®</sup> test into their rejection surveillance protocols starting at earlier post-transplant intervals.<sup>249</sup> Recent studies have investigated the utility of peripheral blood GEP for earlier rejection monitoring after HT. The E-IMAGE study (early IMAGE) was a randomized trial of GEP versus EMB which enrolled 60 patients between 2 to 6 months after HT. Patients were followed with GEP or EMB, and a GEP score  $\geq 30$  between the 2 and 6th month and  $\geq 34$  after the 6<sup>th</sup> month post-transplant prompted a follow-up EMB. There were no significant differences in the primary endpoint of death/retransplantation, rejection with hemodynamic compromise, or graft dysfunction at 18 months post-transplant. Additionally, there was no difference in the first year maximal intimal thickness by intravascular ultrasound.<sup>250</sup> In the CARGO II observational study, a GEP score  $< 34$  could identify patients at low risk for rejection, even early ( $\geq 2$ -6 months) after transplantation.<sup>251</sup> The impact of GEP-guided surveillance on long-term clinical outcomes still needs further evaluation.

*Donor derived cell-free DNA.* Cell-free DNA are short, extracellular fragments of DNA released into the circulation from both the donor graft and recipient cells. During both cellular and antibody mediated rejection, a greater amount of donor derived cell free DNA (DD cf-DNA) is released in the blood from the damaged graft in the setting of myocyte necrosis and apoptosis. Shotgun sequencing of the purified DNA allows for quantification of recipient versus donor DNA fragments through SNPs (single nucleotide polymorphisms) which vary between donor and recipient.<sup>252</sup> A rise in the percentage of DD cf-DNA in the recipient's blood has been observed before acute rejection.<sup>253–256</sup> Promising results have been reported in observational studies in adults and some teenagers. As a result, some centers have adopted DD cf-DNA for rejection surveillance and to reduce the number of EMBs during three months to 1-year post-transplantation.<sup>255, 257</sup>

*T-cell function.* A key event in graft rejection is the activation and proliferation of the recipient's lymphocytes, particularly T-cells which are also detrimental to long-term transplant outcome. Pharmacodynamic monitoring by direct measurement of T-cell activation and proliferation therefore has the potential to personalize immunosuppression. The FDA-approved ImmuKnow<sup>™</sup> assay evaluates immunoreactivity by stimulating T-cells with phytohemagglutinin (PHA) and measuring ATP production in the cell mix. A retrospective analysis of 296 heart transplant recipients demonstrated that values  $< 200$  ng ATP/mL were associated with infectious episodes but that the association between higher values and rejection was inconclusive due to the small number of rejection episodes observed among the heart transplant cohort.<sup>258</sup> In pediatric heart transplant recipients, the immune cell function assay was not found to be a reliable clinical tool to predict infection or rejection or to optimize or personalize immune suppression.<sup>259</sup> A more recent meta-analysis incorporating multiple organ transplants concluded that monitoring T-cell function is not

suitable to identify individuals at risk of rejection or infection.<sup>260</sup> Besides technical limitations (time-consuming, indirect cell function test requiring a cell isolation and 30 h stimulation) the use of a strong mitogen such as PHA may be too overpowering to allow quantification of the immune response outside the extremes of severe rejection or infection and therefore not useful in the mid-range of stable immune suppression. The available data does not allow recommendation of this test in routine practice. The test may, however, be useful in providing information on patients with or at risk of infection.

*Donor specific antibodies.* The development of de novo donor specific antibodies (DSA) after heart transplantation is not uncommon, occurring in up to 25% of recipients at 10 years post-transplantation. The majority of de novo DSA's are directed against Class II or a combination of Class I and II HLA antigens and have been associated with poor post-transplant survival.<sup>261</sup> De novo DSA's, particularly Class II antibodies, persistent antibodies on serial testing, and antibodies appearing more than 1 year after HT have also been shown to predict subsequent antibody-mediated rejection (AMR) and graft loss.<sup>262–264</sup> An international consensus conference was organized in 2016 by ISHLT to review current practices on antibody detection and management in HT, identify best practices, and establish consensus recommendations.<sup>177</sup> Solid-phase assays, such as the Luminesx SAB assay, were recommended to detect circulating antibodies. Post-transplant monitoring for DSA should be minimally performed at 1-, 3-, 6-, and 12 months post-transplant. Thereafter, patients should be monitored annually, except for high-risk patients, who require more frequent surveillance. Consideration should be given to evaluation for non-HLA antibodies in the setting of graft dysfunction, particularly when there is no evidence of HLA antibodies. These include antibodies against MHC class I chain-related polypeptide A (MICA), endothelial cells, and angiotensin receptor (AT-1R) antibodies, which have been associated with alloreactivity, CAV, and AMR. Participants additionally recognized that the identification of antibodies of clinical relevance and the optimal approach to the management of antibodies post-transplantation remained an area of uncertainly and active investigation.

*Emerging biomarkers.* *microRNAs* are a class of small non-coding RNAs that regulate gene expression and play an important role in many CV diseases. They can be found in tissue, blood, and other body fluids such as urine. Several types of microRNA and their expression levels in tissue and blood are related to the immunological profile of the patient. Four microRNAs (miR-10a, miR-31, miR-92, and miR-155) showed differential tissue and serological expression between rejecting and normal cardiac allografts and were able to discriminate between patients with and without acute rejection.<sup>265</sup> Their levels are stable in the blood and thus they have been proposed as promising diagnostic biomarkers, but further data is needed.<sup>266</sup>

*Exosomes and other nanoparticles or microvesicles* have been identified as potential vectors between cells by

carrying messenger RNAs, microRNAs, and proteins and releasing their cargo when they fuse with the target cells, thus regulating those cells at the posttranscriptional level with the potential of modulating the immunological profile of the patients. The characterization of serum exosome content has shown promise in rejection monitoring.<sup>267</sup>

### **Cardiac MRI in the diagnosis of transplant rejection**

Cardiac MRI (CMR) offers multiple potential advantages in the diagnosis of transplant rejection using volumetric measurement, function including strain imaging, perfusion imaging, and tissue characterization including T1 and T2 mapping, extracellular volume (ECV) measurement, late gadolinium enhancement (LGE), and spectroscopy. LGE correlating with scar is commonly found in transplanted hearts regardless of rejection status and associated with poor outcomes but is insufficient as a single marker of transplant rejection or cardiac allograft vasculopathy.<sup>268–270</sup> T1 mapping has emerged as a potential technique that can characterize transplant rejection both by elevations in native values, as well as identification of diffuse fibrosis and/or late graft dysfunction phenotype through ECV measurement.<sup>271–273</sup> Elevations in T2 values correlating with edema in acute rejection have been observed in multiple studies over many years and hold promise.<sup>274</sup> Limitations including small study populations, a lack of randomized control trials, variability of CMR techniques, and multiple phenotypes of transplant rejection have led to lack of consensus about which single CMR technique may provide utility. Multiparametric assessment incorporating the different strengths of CMR, particularly T2 mapping and ECV, may offer a way to optimize the use of CMR for transplant rejection.<sup>271, 275–277</sup> At this time, insufficient evidence is present to advocate for routine use of CMR for the diagnosis of transplant rejection, though there may be utility particularly in cases of biopsy negative rejection or suspected CAV.

### **Noninvasive monitoring in pediatric patients**

Given the less favorable risk-to-benefit ratio for EMB surveillance outlined above much effort has been put into improving noninvasive monitoring for rejection in children, especially during infancy and early childhood. The limited available data on biomarker-monitoring in children is outlined in the respective sections above. Echocardiography is routinely used as a complementary or alternative surveillance technique for rejection monitoring in patients without symptoms or clinically suspected rejection and long-term outcomes in centers relying on this type of monitoring with no or very low frequency surveillance-EMB are not different from those reported by high frequency biopsy centers.<sup>240, 242, 278</sup> While systolic function and various indices have been used since the 1990s with moderate sensitivity and specificity for rejection detection, the use of functional echocardiogram including Doppler-indices and a recently described tissue Doppler index have shown better predictive values for rejection and graft deterioration. Lu et al.<sup>279, 280</sup>

found combinations of flow and tissue doppler measures (E/E', E/LV, diastolic strain) to show good correlation with elevated wedge-pressures, which previously were identified to be an excellent invasive predictor for graft survival in patients with any degree of graft vasculopathy. However, the predictive value for acute rejection of any of the assessed echo-parameters was modest, with LV-ejection fraction using 2D area and length tracing showing the best results with a sensitivity of 100%, however, poor specificity of 40%. A recent European study found overall reasonable performance for longitudinal strain assessments with rejection 2R or higher, especially when combining LV and RV findings. LV longitudinal strain <15.5% and free wall RV longitudinal strain <17% had a 98.8% negative predictive value for ACR; however, the positive predictive values were below 45%, making these parameters more useful to exclude the presence of rejection.<sup>281</sup> Hernandez et al. proposed an index combining M-mode measures of the left ventricular wall thickness with tissue doppler measures. This detected rejection with a sensitivity, specificity and predictive values all ranging above 90% in a small series of 47 transplanted children with 11 rejection episodes. They also found that response to ACR therapy was reflected in improving index values.<sup>282</sup> The results of both studies applied to patients beyond 3 months post-transplant. Whether these assessment-modalities can be validated in clinical practice has to be determined. The previously described echo indices are hampered by inter-observer variability. Further, applied clinical value was often not equally successful in follow-up studies or reports from other centers trying to implement these novel approaches.

Similar to the adults, cardiac MRI shows a good sensitivity and specificity for detection of acute rejection in transplanted children; however, it requires general anesthesia in younger children, is time consuming and expensive. In patients requiring general anesthesia for MRI the risks of the procedure minimize the advantage over EMB monitoring and the usefulness as a modality for routine monitoring.

In summary, there is good evidence for the value of echocardiography-based monitoring as a noninvasive tool to identify rejection, however, given limitations of predictive value and specificity it cannot fully replace EMB which should still be used in cases of suspicion or to confirm echo-suspected rejection. Depending on the patient's risk assessment in regard to rejection probability and also adverse effects of EMB, an echo-supported minimization of biopsy surveillance appears the optimal approach.

### **Rejection monitoring for ABO incompatible transplanted children**

Using donor hearts across blood group barriers considered incompatible in adults (A or AB into B-recipient; B or AB into A recipient; A, B or AB into O recipient) has evolved from an experimental approach based on pioneer center experiences, into routine practice offered for children in the first 2 years of life. A recent PHTS registry analysis showed up to 70% of children < 2 years of age were

listed for ABOi with 40% receiving an ABOi heart transplant.<sup>188, 190, 191, 283, 284</sup> This approach has significantly reduced time to transplantation, especially blood group O patients.<sup>191, 285</sup> Studies have consistently shown that the incidence of acute rejection and graft vasculopathy are similar or lower after ABOi than ABO compatible transplantation using similar immune suppressive regimens. There is

virtually no ABO-related antibody mediated rejection, suggesting that no intensified monitoring or increased frequency of EMB is required after ABOi transplant.<sup>190, 286, 287</sup> While a small number of older children and selected adults have received intentional ABOi heart transplantation currently there is insufficient data to allow clear recommendations for these patients.<sup>195, 288</sup>

## Topic 1 Rejection Surveillance

### Recommendations for Rejection Surveillance by Endomyocardial Biopsy in Heart Transplant Recipients

#### 2010 Prior Guideline Recommendation

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.

Class IIa, Level of Evidence C

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

Class IIa, Level of Evidence C

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.

Class IIa, Level of Evidence C

After the first postoperative year, EMB surveillance for an extended period of time (e.g., 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 the risk of death in African American recipients.

Class II, Level of Evidence C

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.

Class IIb, Level of Evidence C

#### New Recommendation

#### 2023 Guideline Update Recommendation

Continuing approval without change

It is reasonable to perform periodic EMB during the first 3 to 12 postoperative months for surveillance of HT rejection

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

The standard of care for adolescents should be similar to adults, including surveillance EMB for heart allograft rejection for 3 to 12 months after HT. In younger children, especially infants, the risks associated with EMB and required general anesthesia may outweigh the surveillance benefit for comparably rare acute rejection; therefore, it is reasonable to use a combination of noninvasive screening methods (echocardiography, ECG, biomarkers) instead.

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

After the first postoperative year, it is reasonable to continue EMB surveillance in patients who are at higher risk for late acute rejection. This group includes HT recipients with donor-specific antibodies (DSA), a history of recurrent acute rejection, calcineurin-inhibitor free immunosuppression, reduced immunosuppression due to post-transplant malignancy or chronic infection, African American descent.

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

Routine EMB later than 5 years after HT are not recommended. EMB should be performed only for cause in patients with signs or symptoms of cardiac allograft dysfunction

**Class III, Level of Evidence: C**

Children receiving ABO incompatible cardiac allografts in the first 2 years of life with isohemagglutinin titers toward the donor blood group below 1:32 and without elevated titers post-transplant do not require more frequent EMB or non-invasive monitoring compared to recipients of ABO compatible organs.

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

### Recommendations for the Noninvasive Monitoring of Acute Heart Transplant Rejection

#### 2010 Prior Guideline Recommendation

In centers with proven expertise in VER monitoring, intramyocardial electrograms recorded noninvasively with telemetric pacemakers can be used for rejection surveillance in patients at low risk for rejection.

Class IIa, Level of Evidence: C

#### 2021 Guideline Update Recommendation

Ventricular evoked responses (VER) monitoring for rejection surveillance is no longer recommended as the technology has become obsolete.

**Class III, Level of Evidence: C**

(continued on next page)

*(Continued)*

## Topic 1 Rejection Surveillance

## Recommendations for Rejection Surveillance by Endomyocardial Biopsy in Heart Transplant Recipients

## 2010 Prior Guideline Recommendation

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.

Class IIa, Level of Evidence: B

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

Class IIb, Level of Evidence: C

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

Class III, Level of Evidence: C

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

Class III, Level of Evidence: C

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

Class III, Level of Evidence: C

The use of BNP, troponin I or T, or CRP levels for acute heart allograft rejection monitoring is not recommended.

Class III, Level of Evidence: C

**New recommendation**

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

Class III, Level of Evidence: C

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

Class III, Level of Evidence: C

**New Recommendation**

## 2023 Guideline Update Recommendation

Gene Expression Profiling (GEP) (i.e., Allomap) of peripheral blood can be used in low-risk patients between 2 months and 5 years after HT to identify adult recipients who have low risk of current ACR to reduce the frequency of EMB. Data in children does not allow a general recommendation of GEP as a routine tool at present

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

In pediatric patients, echocardiography, especially detailed assessment of diastolic function, shows reasonable correlation with significant acute rejection; however, it should not be considered as a sole surveillance method in patients who have a low risk of EMB complications. In younger children, echocardiographic surveillance represents an alternative monitoring modality to avoid or reduce the frequency of EMB.

**Class IIb, Level of Evidence B**

Continuing approval without change

Echocardiography may be an acceptable rejection monitoring strategy in patients at low risk for acute rejection and in whom EMB is not possible (i.e., tricuspid valve replacement or difficult vascular access). **Class IIb, Level of Evidence: C**

MRI with gadolinium enhancement may be used as an adjunct modality in patients with unexplained graft dysfunction and low-grade or absent histologic evidence of rejection on EMB.

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

It is reasonable to integrate biomarkers such as BNP and high-sensitivity troponins into a rejection monitoring strategy to identify higher risk patients who may benefit from additional evaluation for ACR, AMR, or CAV.

**Class IIb, Level of Evidence C**

Post-transplant monitoring for DSA should be performed at 1, 3, 6, and 12 months postoperatively and annually thereafter. Sensitized patients should be monitored more frequently.

**Class IIa, Level of Evidence C**

The use of systemic inflammatory markers such as C-reactive protein (CRP) for acute heart allograft rejection monitoring is not recommended.

**Class III, Level of Evidence: C**

In younger children, especially infants, the risks associated with EMB and required general anesthesia may outweigh the surveillance benefit for comparably rare acute rejection; therefore, it is reasonable to use a combination of noninvasive screening methods (echocardiography, ECG, biomarkers) instead.

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

Use of the immune cell function assay (ImmuKnow) cannot be recommended in adult and pediatric heart transplant recipients for rejection monitoring.

**Class III, Level of Evidence B**

## Topic 2: Monitoring of immunosuppressive drug levels

### Pharmacology/pharmacokinetics and immunosuppression monitoring

**Everolimus (EVL) & Sirolimus (SRL) Target levels in combination with other immunosuppressants.** Clinical trials in recent years have investigated mammalian target of rapamycin (mTOR) inhibitors either in combination with reduced exposure CNI, or as part of a CNI-free regimen (i. e., mTOR + mycophenolate product). Data from these studies can guide clinicians in determining the optimal target concentration ranges and timing of introduction of these agents (Tables 6, 7 and 8).

#### Everolimus

Several clinical trials have demonstrated immunosuppressive regimens using EVL C<sub>0</sub> 3 to 8 ng/mL with reduced exposure cyclosporine (CYA) comparable in efficacy to standard dose CYA and mycophenolate mofetil (MMF).<sup>289–291</sup> While less has been published on EVL with dose reduced tacrolimus (TAC), one maintenance study in thoracic transplant recipients demonstrated similar efficacy between patients 1 year post transplant receiving either a standard CYA or TAC-based regimen, or reduced CNI with EVL C<sub>0</sub> 3 to 8 ng/mL.<sup>292</sup> Higher EVL doses targeting a C<sub>0</sub> 6 to 12 ng/mL in combination with CNI were associated with increased early mortality.<sup>289</sup> However, in CNI-free regimens slightly higher EVL exposure targets have been used. Patients in the CNI-free arm of the SCHEDULE study received reduced exposure CYA with EVL initially targeted to C<sub>0</sub> 3 to 6 ng/mL, increased to C<sub>0</sub> 6–10 ng/mL following CYA withdrawal 7 to 11 weeks post-transplant. Compared with patients continued on standard dose CYA/MMF, a higher incidence of BPAR was observed in the CNI-free group in the first 12 months, but not between months 12–36, and cardiac function was not affected at 12, or 36 months follow-up.<sup>293, 294</sup> In the MANDELA trial, where EVL exposure was targeted to C<sub>0</sub> 5 to 10 ng/mL, the CNI-free group had significantly more rejection than those on reduced CNI plus EVL (21.1% vs. 6.8%,  $p = 0.015$ ), and it was noted that 40% of these patients had an EVL C<sub>0</sub> <5 ng/mL before BPAR.<sup>295</sup>

#### Sirolimus

Earlier studies in de novo cardiac transplant recipients demonstrating the immunosuppressive efficacy of SRL in combination with CNI used a target SRL level C<sub>0</sub> 8 to 18 ng/mL in combination with CYA, and SRL C<sub>0</sub> 4 to 12 ng/mL in combination with TAC.<sup>296, 297</sup> Later studies using SRL in CNI-free regimens used varying exposure target C<sub>0</sub> ranges between 6 and 15 ng/mL. Two studies indicated similar immunosuppressive efficacy compared with CNI based regimens, one in cardiac transplant recipients

with chronic renal failure using SRL C<sub>0</sub> 8 to 14 ng/mL; the other, a retrospective, observational study of patients switched at least 3 months post-transplant to CNI-free immunosuppression, with SRL C<sub>0</sub> 10 to 14 ng/mL.<sup>298</sup> No difference in rates of treatable cellular rejection or AMR were identified between groups, and SRL was also associated with significantly lower all-cause mortality ( $p = 0.0002$ ).<sup>299</sup> Another study targeting SRL C<sub>0</sub> between 7 and 15 ng/mL found a numerically higher rate of acute rejection in the CNI-free group compared with those who continued on CNI.<sup>300</sup> Over a third of patients who rejected in the SRL group had at least one measured SRL C<sub>0</sub> below 7 ng/mL before the rejection episode, although a post-hoc analysis did not indicate that low SRL trough concentration overall was associated with BPAR.<sup>300, 301</sup> Higher incidences of adverse effects including increased triglycerides, acne, rash, diarrhea, and infection were observed in patients receiving SRL based CNI-free suppression,<sup>299–301</sup> where higher target SRL levels were used.

**Pediatric experience.** Due to the lack of evidence and controlled studies, published experience is rare for the use of mTOR in pediatric heart transplantation. The therapeutic concepts and respective literature are outlined in topic 3. In the absence of controlled trials, recommendations for target levels are based on expert opinion and extrapolation from adult studies. However, as for any immunosuppressive regimen adult studies do not fully reflect the needs in pediatric patients. Particularly, younger children were found to have better graft acceptance than anytime later in life reflected in lower rates of rejection, CAV, longer graft survival and ability to accept ABO incompatible organs. However, they experience a higher incidence of adverse effects of immune suppression such as PTLD and atopic disorders.<sup>302, 303</sup> Accordingly lower target levels and less aggressive immunosuppressive combinations have been used and clinically thought to be safe.<sup>304</sup> Similar to the adult experience, two therapy concepts for the use of mTOR inhibitors are followed, one is CNI reduced, the other is CNI free: (1) CNI-reduced regimens have been used in pediatric patients with progressive renal failure or those with PTLD or presumed high risk thereof. This approach aims towards reducing CNI-toxicity at the price of lower intensity overall immune suppression and was found to be safe and without increased rate of rejection in small case series.<sup>305–307</sup> The randomized, controlled multicenter TEAMMATE (Tacrolimus/ Everolimus vs. Tacrolimus/MMF in Pediatric Heart Transplant Recipients Using the MATE Score) trial is comparing EVR/low dose Tac to Tac/MMF and will evaluate CAV, nephrotoxicity, BPAR and graft dysfunction (all cause) (<https://clinicaltrials.gov/ct2/show/NCT03386539>). The target range for both, CNI and mTOR inhibitor are typically towards the lower target range with a combined level not exceeding the 10 to 14ng/mL range. (2) In CNI-free regimes the mTOR inhibitor represents the more potent drug, in combination with an antiproliferative agent (usually MMF), and target levels aim for the higher end of the

therapeutic range. There is still a demand for published clinical evidence and long-term experience for this approach, which is used as “off-label” treatment in some countries.

### Target levels of CNIs with mTOR inhibitors in adult recipients

Immunosuppressant regimens combining mTOR inhibitor with CNI at reduced exposure, have demonstrated comparable efficacy compared with regimens based on standard dose CYA and MMF.<sup>289, 290, 292, 298</sup> Renal benefits have also been observed. Whether mTOR was introduced early or later post cardiac transplant, several studies aimed for CNI exposure reductions of 30 to 70% from baseline.<sup>292, 298</sup> In combination with EVL, CYA C<sub>0</sub> targets used ranged between 150 and 350 ng/mL within the first 2 months post-transplant, 75 to 200 ng/mL for months 3 to 6, and 50 to 100 ng/mL from month 6 onwards, see Table 4.<sup>289, 290, 295, 308, 309</sup> TAC C<sub>0</sub> targets used in combination with mTOR inhibitors varied depending on time after cardiac transplant, ranging between 3-8 ng/mL.<sup>292, 295, 310, 311</sup>

### Mycophenolate

Mycophenolate pharmacokinetics are complex, and the optimal method to estimate mycophenolic acid (MPA) exposure is still debated. Correlation between C<sub>0</sub> and total MPA exposure is poor<sup>312</sup> and MPA exposure is also affected by concomitant immunosuppressive agents, such as CS and the choice of CNI.<sup>313</sup> Suggested therapeutic target levels for MPA may vary depending on the formulation used, as concentration-time profiles of MPA exposure from mycophenolate mofetil (MMF) and enteric-coated mycophenolate sodium (EC-MPS) differ. Peak plasma

concentrations occur 2 to 3 hours following oral administration of EC-MPS (vs 0.5-2 hours for MMF), due to a delayed absorption phase, and MPA C<sub>0</sub> is also higher and more variable with EC-MPS.<sup>312, 314</sup> These higher troughs do not correlate with increased total drug exposure due to the altered PK profile of MPA from EC-MPS and therefore cannot be used to assess exposure and guide dosing in patients receiving this formulation of mycophenolate.

### Tacrolimus pharmacogenetics

The pharmacokinetic variability of immunosuppressants is also influenced by genetic polymorphisms. The association between CYP3A genotypes and TAC pharmacokinetics has been investigated in both adults and children, demonstrating that transplant recipients who are expressors of CYP3A5 have higher TAC dose requirements than non-expressors. Frequency of CYP3A5 expression is distinct amongst ethnic groups, and genotype-guided dosing may assist TAC dose optimization in cardiac transplant recipients, particularly in the early postoperative period.<sup>315-319</sup>

### Drug interactions

Many of the immunosuppressive agents, particularly the CNIs and mTOR inhibitors, undergo metabolism by CYP450 and p-glycoprotein, and there exists a high potential for drug interactions and changes in immunosuppressant levels which may lead to toxicity through excessive exposure, or potential graft rejection with sub-therapeutic levels. It is important to ensure that if an interacting agent (Table 5) is *added or withdrawn* to existing therapy, close monitoring of immunosuppressant drug levels and dose adjustments are made to avoid any adverse outcomes.

**Table 4** Recommended mTOR Inhibitor & CNI Target Levels

Adults				
IS regimen	Everolimus (ng/mL)	Sirolimus (ng/mL)	Cyclosporine (Time post-tx) (ng/mL)	Tacrolimus (Time post-tx) (ng/mL)
CNI + mTOR inhibitor	3-8	4-12	75-200 (3-6 months) 50-100 (> 6 months)	3-8 (> 6 months)
CNI-free (e.g., mTOR + MMF)	6-10	8-15		
Pediatrics <sup>a</sup>				
IS regimen	Everolimus (ng/mL)	Sirolimus (ng/mL)	Cyclosporine (Time post-tx) (ng/mL)	Tacrolimus (Time post-tx) (ng/mL)
CNI + mTOR inhibitor	3-6	4-7	100-200 (3-6 months) 60-120 (> 6 months)	4-8 (> 6 months)
CNI-free (e.g., mTOR + MMF)	3-8	5-8		

<sup>a</sup>Aim for higher end of range when using mTOR to intensify immune suppression for CAV prevention in high-risk patients; aim for lower end of range when targeting reduced intensity immune suppression for PTLD, frequent infections, or renal failure.



## Topic 2: Monitoring of Immunosuppressive Drug Levels

## 2010 Prior Guideline Recommendation

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

Class I, Level of Evidence: B

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.

Class IIa, Level of Evidence: B

Measurement of 12-hour trough CYA concentration is the recommended form of therapeutic drug monitoring for routine clinical use. The target levels are dependent upon 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 AZA or an 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 onward.

Class IIa, Level of Evidence: C

At present, CYA trough concentration targets when CYA is used in combination with PSIs and mTOR inhibitor agents have not been adequately determined.

Class IIa, Level of Evidence: C

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 an MPA preparation, TAC trough concentration targets range between 10 and 15 ng/mL during the early postoperative 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. Class IIa, Level of Evidence: C

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

Class IIa, Level of Evidence: C

Therapeutic drug monitoring for PSIs using trough concentration levels is recommended for SRL and 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 levels range for EVL between 3 and 8 ng/mL. The corresponding optimal trough level range for SRL is 4 to 12 ng/mL. Class IIa, Level of Evidence: B

## 2023 Guideline Update Recommendation

Continuing approval without change

Continuing approval without change

Continuing approval without change

When used in combination with mTOR inhibitors, CYA trough concentration targets may be 40-50% lower than those used in regimens with AZA or an MPA preparation.

When used in combination with mTOR inhibitors, target CYA trough concentration ranges of 75-200 ng/mL for months 3 to 6, and 50-100 ng/mL for month 6 onward may be considered.

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

Continuing approval without change

When used in combination with mTOR inhibitors, TAC trough concentration targets may be 40-50% lower than those used in regimens with AZA or an MPA preparation. Target trough concentrations early post-transplant have not been adequately established. After 6 months, a target TAC trough concentration between 3 and 8 ng/mL may be considered.

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

Therapeutic drug monitoring for PSIs (mTOR inhibitors) using trough concentration levels is recommended for SRL and EVL. Levels should be measured at least 5 days after adjustment of the dose, when a new steady state is achieved.

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

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*(Continued)*

## Topic 2: Monitoring of Immunosuppressive Drug Levels

## 2010 Prior Guideline Recommendation

## 2023 Guideline Update Recommendation

**New Recommendation**

When used in combination with CYA, the optimal trough target levels range for EVL between 3 and 8 ng/mL.  
(Class IIa, Level of Evidence: B)

When used in combination with TAC, a trough target levels range for EVL between 3 and 8 ng/mL is reasonable.  
(Class IIa, Level of Evidence: C)

When used in a CNI-free regimen, a trough target levels range for EVL between 6 and 10 ng/mL is reasonable.

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

**New Recommendation**

When used in combination with a CNI, the optimal trough level range for SRL is 4 to 12 ng/mL. (Class IIa, Level of Evidence: B)

When used in a CNI-free regimen, a trough target level range for SRL between 8 and 15 ng/mL is reasonable.

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

**New Recommendation**

For pediatric HT recipients, when used in combination with a CNI, a trough target levels range for EVL between 3 and 6 ng/mL is reasonable. The corresponding trough target levels range for SRL is between 4 and 7 ng/mL. For pediatric HT recipients receiving a CNI-free regimen, a trough target levels range for EVL between 3 and 8 ng/mL is reasonable. The corresponding trough target levels range for SRL is between 5 and 8 ng/mL.

Aiming for the higher end of the range can be beneficial when using an mTOR inhibitor to intensify immune suppression for CAV prevention in high-risk patients. Aiming for the lower end of the range is reasonable when targeting reduced intensity immune suppression for PTLD, frequent infections, or renal failure.

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

There is 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 (e.g., infants and young children), and to assess medical compliance

Class IIa, Level of Evidence: C

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.

Class IIb, Level of Evidence: C

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. Class IIb, Level of Evidence: C

Continuing approval without change

Replacement of twice-daily TAC with once-daily extended-release TAC dosing may be considered in selected situations (e.g., compliance, side effects). Should a patient require the once-daily formulation, appropriate monitoring should be used to ensure maintenance of appropriate levels and preserved heart allograft function.

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

In patients with a therapeutic 12-hour trough concentration for twice-daily TAC but evidence of potential drug-related toxicity or reduced efficacy (rejection), measuring AUC may be considered an alternative method to assess drug exposure and adjust TAC doses. For patients who target TAC trough levels are difficult to reach, genotyping may be useful to ascertain rapid metabolizer status, and guide dosing.

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

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*(Continued)***Topic 2: Monitoring of Immunosuppressive Drug Levels****2010 Prior Guideline Recommendation**

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/L is considered to be subtherapeutic.  
Class IIb, Level of Evidence: C

Dose adjustments and frequency of therapy with polyclonal antibodies (e.g., ATG) 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<sup>3</sup> or absolute total lymphocyte counts < 100 to 200 cells/mm<sup>3</sup>.  
Class IIb, Level of Evidence: C

In pediatric HT recipients, CYA C2 monitoring may be performed instead of C0 in centers with extensive experience with this form of monitoring.  
Class IIb, Level of Evidence: C

Class IIb, Level of Evidence: C

As in adults, routine monitoring of SRL and EVL at C0 is recommended also in children. Class IIb, Level of Evidence: C

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

Class III, Level of Evidence: C

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

Class IIb, Level of Evidence: C

**2023 Guideline Update Recommendation**

In selected situations (rejection, infection, renal failure, change in concomitant immunosuppression, malnutrition, and certain ethnic populations) where it is suspected that altered MMF exposure contributes to heart allograft dysfunction or drug toxicity, measurement of trough MPA levels may be used to guide drug dosing. In such cases of graft dysfunction, a MPA level of < 1.5 mg/L is considered subtherapeutic. Trough MPA levels should not be used to guide dosing in patients receiving EC-mycophenolate sodium.  
**Class IIb, Level of Evidence: C**

Dose adjustments and frequency of therapy with polyclonal antibodies (e.g., ATG) used as induction therapy can be monitored with regular measurement of CD3 or CD2 counts with the goal of maintaining the CD2 or CD3 count between 25 and 50 cells/mm<sup>3</sup> or absolute total lymphocyte counts < 100 to 200 cells/mm<sup>3</sup>.  
**Class IIb, Level of Evidence: C**

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

**Recommendation removed.**

Continuing approval without change

Continuing approval without change

**Recommendation removed.**

**Recommendations for the Monitoring of Immunosuppressive Drug Levels for Pediatric Heart Transplant Recipients****2010 Prior Guideline Recommendation**

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 nonsensitized infant recipients.  
Class IIa, Level of Evidence: C

Class IIa, Level of Evidence: C

There is insufficient data to support routine monitoring of MPA levels. However, intermittent monitoring is reasonable when there is ongoing rejection, doubts about adequacy of dosing (e.g., infants and young children) and to assess medical compliance. Class IIa, Level of Evidence: C

CYA C2 monitoring may be performed in lieu of C0 in centers with extensive experience with this form of monitoring. Class IIb, Level of Evidence: C

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

Class IIb, Level of Evidence: C

**2023 Guideline Update Recommendation**

TAC and CYA should be monitored using C0 levels, when twice-daily dosing is used. Target levels are comparable to those in adults, but lower targets may be used in patients believed to be at low risk for acute rejection, such as nonsensitized infant HT recipients.  
**Class IIa, Level of Evidence: C**

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

Continuing approval without change

**Recommendation removed.**

Continuing approval without change

**Table 5** Drugs That Affect the Levels of Tacrolimus, Cyclosporine, Sirolimus, or Everolimus

Decrease immunosuppression levels	Increase immunosuppression levels
<b>Antiepileptics</b>	<b>Antifungals</b>
Carbamazepine	Clotrimazole
Fosphenytoin	Fluconazole
Phenobarbital	Isavuconazole
Phenytoin	Itraconazole
	Ketoconazole
	Posaconazole
	Voriconazole
<b>Antimicrobials</b>	<b>Antimicrobials</b>
Caspofungin	Clarithromycin
Nafcillin	Erythromycin
Rifabutin	Metronidazole and tinidazole
Rifampin	
Rifapentine	
<b>Antiretroviral therapy</b>	<b>Antiretroviral therapy</b>
Efavirenz	Protease inhibitors (general)
Etravirine	Cobicistat
Nevirapine	Darunavir
	Fosamprenavir
	Indinavir
	Nelfinavir
	Ritonavir
	Saquinavir
	Tipranavir
	Antivirals
	Letermovir
<b>Monoclonal antibodies</b>	<b>Direct acting antivirals for Hepatitis C</b>
Tocilizumab	Daclatasvir
	Glecaprevir-Pibrentasvir
	Grazoprevir-Elbasvir
	Ledipasvir-(Sofosbuvir)
	Velpatasvir-(Sofosbuvir)
	Voxilaprevir-Velpatasvir-(Sofosbuvir)
<b>Cardiovascular</b>	<b>Cardiovascular</b>
Bosentan	Amiodarone
	Diltiazem
	Verapamil
<b>Others</b>	<b>Others</b>
Aprepitant	Cimetidine
Deferasirox	Fluvoxamine
Modafinil	Glipizide
St. John's wort	Glyburide
Thalidomide	Imatinib
Ticlopidine	Nefazodone
	Rilonacept
	Theophylline
	Turmeric
	<b>Nutraceuticals</b>
	Bitter orange
	Grapefruit

### Topic 3: Principles of immunosuppression and recommended regimens

#### Introduction of mTOR Inhibitors – timing

The use of mTOR inhibitors in de novo, and later introduction into immunosuppressive regimens post-transplant has been investigated in several trials since 2010 with respect to their effects on CAV, renal function, immunosuppressive efficacy, and adverse events.

CAV. Benefits on CAV have been seen with early introduction of mTOR, as observed in de novo cardiac transplant recipients receiving EVL with reduced exposure CYA, who after 1 year had significantly reduced intimal proliferation on IVUS, compared with patients receiving CYA/MMF.<sup>289</sup> The SCHEDULE study also demonstrated a significantly lower incidence and progression of CAV up to 7 years follow up in patients who post-transplant initially received reduced exposure CYA and EVL followed by CNI withdrawal at weeks 7 to 11, compared with those who continued standard CNI based immunosuppression.<sup>293, 294, 320</sup> Similar benefits were seen in patients converted from CNI based immunosuppression to a CNI-free SRL regimen at a median of 0.7 years post-transplant, with significantly reduced progression in plaque volume, lower rates of high-grade CAV, and fewer fatal, and nonfatal CAV related events. The greatest benefit was attained in those who were converted 6 to 24 months post-transplant, compared to those who were switched  $\geq 2$  years later.<sup>299</sup>

Renal function. Superior renal function was demonstrated in patients receiving de novo EVL on the CNI-free arm of the SCHEDULE study, with significantly higher measured GFR at 1 year, 3 years, and maintained up to 7 years post CNI withdrawal.<sup>293, 294, 320</sup> A significantly higher eGFR at 18 months was also observed in patients randomized to EVL based CNI free immunosuppression 6 months post cardiac transplant, compared with those randomized to continue EVL with low dose CNI.<sup>295</sup> Later introduction of mTOR can also offer benefits on renal function, as seen in thoracic transplant patients with deteriorating renal function given EVL with reduced CNI one year post transplant. These patients demonstrated a higher measured GFR after one year, with a greater benefit seen in patients converted to EVL earlier post transplant (within 5 years), and no improvement in cardiac transplant recipients converted more than 8 years post transplant.<sup>292, 321</sup> Long term follow up in cardiac transplant recipients demonstrated the significant improvement in renal function can be maintained for at least 5 years.<sup>322</sup> Another study highlighted renal benefit could be attained in patients switched to EVL and reduced CNI 1 to 4 years post transplant, particularly in those without baseline proteinuria, although in contrast, a substudy of SCHEDULE found degree of albuminuria was not associated with deteriorating renal function, and no further increase in albuminuria was observed with continued EVL use after week 7, following CNI withdrawal.<sup>309, 323</sup>

A number of studies found comparable renal function whether mTOR was introduced early or later post transplant.<sup>299, 305, 309</sup> In one study finding de novo EVL with reduced CYA inferior to MMF and standard CYA for eGFR, a post-hoc analysis identified suboptimal reduction of CYA exposure in the EVL group a possible contributor to inferior renal function.<sup>289</sup>

**Immunosuppressive efficacy.** Comparable efficacy has been demonstrated between de novo EVL with reduced exposure CYA and standard dose CYA with MMF, as well as early and delayed EVL introduction in combination with reduced exposure CYA.<sup>289, 309</sup> However, compared with standard CNI based immunosuppressive regimens, numerically higher rates of biopsy proven acute rejection (BPAR) have been observed in patients receiving CNI-free mTOR based therapy.<sup>292, 295, 300</sup> In studies involving early CNI discontinuation (7-24 weeks), this was statistically significant, despite patients also receiving ATG induction, with the rate and severity of increased BPAR more marked in the study where CNI was withdrawn earlier at weeks 7 to 11, compared to CNI withdrawal at 6 months.<sup>294, 295</sup> However, the increased incidence of BPAR observed during year 1 in the SCHEDULE trial did not compromise long term cardiac function compared with the CNI control arm.<sup>293, 294, 320</sup> Numerically higher rates of acute rejection have also been observed in late conversion to mTOR (1-8 years),<sup>300</sup> but a post hoc analysis of this SRL conversion study found low MMF doses were associated with increased incidence of BPAR.<sup>301</sup> A retrospective analysis of patients switched to a CNI-free SRL regimen at least 3 months post cardiac transplant found no difference in rates of treatable cellular rejection, rejection with hemodynamic compromise, AMR and allograft function compared with those maintained on CNI based therapy.<sup>299</sup> In another retrospective, multicenter analysis of 284 patients converted to EVL based CNI-free immunosuppression a median 8 years post heart transplant, conversion less than 5 years after transplantation, age at conversion  $\leq 50$  years and a history of late rejection before conversion were independently associated with rejection after conversion.<sup>324</sup>

**Adverse events.** Patient tolerance may also influence incorporation of mTOR into immunosuppressive regimens. Several studies have observed higher rates of adverse drug events including pericardial effusion, oral ulcers, interstitial edema, serious adverse events including pneumonia, and study drug discontinuation associated with EVL or SRL use particularly when introduced early post transplant.<sup>289, 299, 300, 308</sup> Higher mortality in de novo heart transplant recipients with EVL use in the first 3 months post-transplant was reported, mainly due to infection, particularly in patients treated with rATG.<sup>289, 299, 300, 308</sup> In contrast, the incidence of adverse events including sternal wound complications were comparable across all arms in the SCHEDULE and MANDELA studies, and in both the SCHEDULE and A2310 studies CMV infection was significantly less frequent in EVL treated patients.<sup>289, 293–295, 320</sup>

## **Pediatric experience**

In children published data on CNI free regimens are limited to small single center retrospective reports with no control groups for various underlying considerations (renal dysfunction, PTLD, high EBV viral load).<sup>305</sup> The referenced study reported a significant improvement of the eGFR after a median observation period of 28 months following switch from a CNI to sirolimus in 15 and everolimus in 4 patients.

Beside the reports mentioned above, an analysis of the prospective multicenter registry of the Pediatric Heart Transplant Society (PHTS) compared 144 heart transplanted children receiving sirolimus for any indication and in any combination therapy with 2080 patients on mTOR free regimens at 1-year post-transplant. Borderline benefits in freedom from infection and CAV for mTOR patients did not persist when patients were propensity matched for clinical characteristics.<sup>325</sup> The heterogeneity of therapeutic approaches and patient characteristics does not allow any clear recommendation regarding use of sirolimus in pediatric heart transplant. More clarity is expected from the ongoing TEAMMATE study discussed above.

## **Considerations for comprehensive assessment of IS in prevention of long-term complications and major adverse transplant events: CAV, renal function, and malignancy**

**CAV and renal function.** Evidence from the studies discussed above suggest early initiation of mTOR has been associated with the greatest benefit in terms of protecting renal function and developing CAV but concerns about the risk of rejection particularly in mTOR regimens that include CNI withdrawal, indicate the importance of careful patient selection and individualization of immunosuppressive therapy.

There are several studies evaluating the efficacy and safety of PCSK9 inhibitors in HTx recipients. Sammour et al reported in 33 HTx recipients treated with PCSK9i and with serial coronary angiography and IVUs that PCSK9i were effective in stabilizing coronary intimal hyperplasia.<sup>326</sup> An ongoing randomized clinical trial (EVOLVD) will assess whether treatment with evolocumab can ameliorate CAV over the first year after heart transplant.<sup>327</sup>

**Malignancy.** Rivinius et al<sup>328</sup> in a retrospective cross-sectional analysis with 381 patients after transplant showed that treatment with mTOR >1 year was associated with a statistically lower risk for the development of noncutaneous malignancy and with a lower cutaneous malignancy recurrence at 2 and 5 years after the initial diagnosis. Asleh et al reported in a large cohort of heart transplant recipients with a mean follow up of 10 years that sirolimus based immunosuppression without CNI was associated with a significantly lower incidence of overall de novo malignancies and postransplantation lymphoproliferative disorders (PTLD). The incidence of the first non melanoma skin cancer (NMSC) after heart transplantation was similar in the sirolimus and CNI groups however sirolimus conversion was associated with significantly decreased risk of subsequent NMSC occurrence.

The main limitation in both studies was drug discontinuation where 15 % of the patients were intolerant.<sup>328, 329</sup>

**Pediatric considerations.** In children PTLD represents over 90% of all neoplasms typically in the form of B-cell lymphomas and in strong association with EBV infection.<sup>48, 330</sup> Therapies are directed by tumor-phenotype, staging, time post-transplant, and comorbidities and include rituximab alone or as part of a chemotherapy protocol. Any described therapeutic approach includes reduced immune suppression with the optimal approach remaining unclear. Commonly the CN1 target trough level range is reduced and concomitant antiproliferative drugs are held at least for the duration of chemotherapy, but mostly for the first year post-treatment.<sup>303, 331</sup> However, neither MMF nor mTOR inhibitors were found to be associated with increased risk of PTLD in any studies, and in vitro data and pathomechanistic considerations suggest a potential benefit of mTOR inhibitors for patients with or at risk of PTLD, however, this is not yet confirmed in clinical studies.<sup>131</sup> The approach of completely discontinuing immune suppression while receiving chemotherapy for PTLD has not resulted in different outcomes for tumor relapse or progression but higher rates of acute rejection compared to maintenance of a baseline monotherapy immune suppression.<sup>331</sup>

**Induction therapy.** The benefit of induction therapy, its impact on survival, and the preference for the induction regimen are still a matter of debate. Although recent observational studies have reported an increase of treated acute rejection episodes in patients without induction therapy than patients treated with ATG and a higher incidence of malignancy-related deaths associated to ATG administration, since 2016 there are no randomized clinical trials evaluating this topic.<sup>332–336</sup>

### **Rituximab induction**

Rituximab has commonly been used in protocols for desensitization, antibody mediated rejection, or PTLD. The use of B-cell depleting therapies at induction in nonsensitized patients undergoing cardiac transplantation has so far been limited.

Data in renal transplantation has had mixed results: One study observed a high rate of biopsy proven acute rejection (BPAR) within the first 3 months post-transplant in patients randomized to rituximab induction versus those receiving daclizumab (83% vs 14%), while another found BPAR incidence comparable between patients receiving single dose rituximab or placebo, but a significantly higher rejection risk in immunologically high-risk patients (PRA>6% or re-transplant) not receiving rituximab.<sup>337, 338</sup>

The CTOT-11 study investigated whether B-cell depletion therapy would attenuate development of CAV in nonsensitized cardiac transplant recipients (PRA <10%).<sup>339</sup> Patients were randomized to rituximab 1000mg IV or placebo on days 0 and 12 post-transplant, with conventional maintenance immunosuppression. There were no significant differences in mortality, treated rejection, or infection rates

between treatment groups. However, paired baseline and 1-year intravascular ultrasound measures demonstrated rituximab induction was associated with accelerated coronary vasculopathy, with the mean change in percent atheroma volume significantly higher in rituximab treated patients ( $p = 0.0019$ ).

### **Induction therapy in pediatric heart transplantation**

There are no prospective randomized trials comparing different induction regimens in children receiving heart transplantation, however, several registry and multicenter study analyses with large patient numbers have recently focused on this topic. The natural limitation of these type of studies are patient selection and clinical biases, as well as potential center effects that impact outcomes. Unanimously these studies found different risk profiles between induction strategies with patients receiving polyclonal induction (ATG) or interleukin 2 receptor antagonist (IL2RA, Basiliximab, or Daclizumab) showing a higher risk profile with overrepresentation of patients with congenital heart disease, HLA sensitization and other factors generally associated with worse outcomes. Studies using data prospectively collected in the PHTS-registry found similar long-term survival and freedom from CAV comparing no induction with any induction, but longer freedom from rejection for either type of induction.<sup>340, 341</sup> Castleberry et al. stratified patients using a previously validated risk score and found that the largest benefit of induction was noticed in lower risk patients. They also noticed longer freedom from infection in IL2RA patients compared to ATG or no induction. In contrast a study using the UNOS database found no survival-benefit for induction with exception of highly sensitized (PRA >50%) patients and another UNOS data-based study found a benefit of ATG over IL2RA in regards to graft survival only for black recipients.<sup>342, 343</sup> Two studies suggested an overall survival advantage of ATG over IL2RA, one using the UNOS and one the ISHLT registry, however, did not take into account differences in clinical demographics including significantly younger age in the ATG group and different follow-up periods between their groups into account.<sup>344, 345</sup> Beside the clinical heterogeneity of the examined cohorts, a potential explanation for controversial findings may also be the exact application of induction therapies: Since IL2RA block the IL2-receptor CD25, which is also highly expressed on regulatory T-cells, application at sufficient time before the transplant surgery (more than 2 h before bypass) appears to be crucial to warrant the suppressive effect during the early activation of the immune response outweighing a potential effect on regulatory T-cells while post-transplant application may fail to provide a benefit.<sup>346</sup> None of the large registry studies has identified a clearly increased risk of PTLD for patients receiving induction therapy, which is in contrast to previous single center studies suggesting a correlation between ATG use and PTLD.

Based on previous single center reports on steroid reduced induction and maintenance protocols a multicenter collaboration was initiated (CTOTC-04) avoiding steroids beyond the first week by using ATG induction. They recently published early outcomes in the lower risk patient

group with absence of donor specific or any HLA antibodies, showing good survival, freedom from rejection and infection up to 1 year after transplantation.<sup>128</sup> Unfortunately, this study was set up as an observational study only without a control group, and can therefore not provide comparison data to other induction strategies.

Data on optimal therapy of highly HLA-sensitized children remains scarce. Some centers perform pretransplant desensitization protocols following the same principles used for post-transplant AMR in heart transplant or desensitization-protocols applied in transplants of other solid organs. While the use of IVIG alone was not found to result in clinically meaningful drop of HLA-sensitization, combination with rituximab and bortezomib effectively reduces PRA and antibody levels.<sup>347–349</sup> However, while this increases the pool of potential donors, data on long-term post-transplant outcomes after desensitization are still missing, hence no clear recommendation for or against this approach can be made at this time.

### **Other therapies in transplantation: Belatacept, tocilizumab**

Outside of induction, the use of immunosuppressive agents with novel therapeutic targets has become of increasing interest in transplantation, although studies in cardiac transplantation have been limited.

Belatacept, a selective T-cell co-stimulation blocker, is a fusion protein which binds to CD80 and CD86 receptors of antigen presenting cells, preventing interaction with CD28 on T cells, thus inhibiting T-cell activation and proliferation. Currently licensed for prophylaxis of organ rejection in renal transplant recipients, belatacept also carries an FDA Black Box warning against use in EBV seronegative patients due to the risk of PTLD.<sup>350</sup>

In a randomized, multicenter study of 660 renal transplant recipients, belatacept-based immunosuppression was associated with significantly higher patient and graft survival and improved renal function compared with a CYA-based regimen, despite an increased incidence of biopsy proven acute rejection observed in belatacept treated patients.<sup>351, 352</sup>

Belatacept use in cardiac transplantation was first described in a 26-year-old female heart transplant recipient experiencing repeated rejection episodes, with a background of questionable compliance. Addition of belatacept resulted in subsequent ISHLT grade 0 endomyocardial biopsies, normal coronary arteries on angiogram, and LVEF 61%, but the patient died of cardiac arrest 7 months later.<sup>353</sup> A retrospective case series of 40 cardiac transplant recipients receiving belatacept as alternative immunosuppression was recently described. Belatacept was introduced for renal rescue in 87.5% of patients, with CNI discontinued in 76% of cases. Rejection rates were significantly different in patients initiated on belatacept > 3 months post-transplant, with 67% of endomyocardial biopsies pre belatacept therapy showing no rejection, compared with 61% post ( $p = 0.0002$ ). More ISHLT grade 2R and 3R rejections were also observed. Mean eGFR increased 1 month after commencing belatacept by mean 59% ( $p = 0.0002$ ) and

remained improved at the end of 24 month mean follow up. No significant difference in infection rate was observed pre and post belatacept initiation, although there was 1 death due to severe fungal lung infection and 1 discontinuation due to multiple infections.<sup>354</sup>

Tocilizumab is a recombinant humanized, anti-human monoclonal antibody (mAb) directed against soluble and membrane-bound interleukin-6 receptor (IL-6R). Interleukin-6 is a proinflammatory cytokine that induces the expression of proteins responsible for acute inflammation, and there is growing evidence for the role of the monocyte - macrophage cells in acute and chronic allograft immunopathology. Studies suggest that Tocilizumab inhibits antibody production, reduces inflammation, and induces Tregs.<sup>355–357</sup> In a phase I/II pilot trial, kidney sensitized recipients unresponsive to IVIG and rituximab were treated with IVIG and tocilizumab. There were no episodes of antibody mediated rejection on protocol biopsies at 6 months and DSAs were eliminated in all but one patient.<sup>358</sup> A second ongoing phase II trial is underway in kidney recipients (NCT02108600). Tocilizumab has also been tested as a rescue therapy for kidney recipients with DSA and AMR who had failed standard of care treatment with encouraging results.<sup>359</sup>

These agents may be promising alternative immunosuppressive treatment options in cardiac transplantation, but further studies are required to establish their safety, efficacy, and long-term outcomes.

### **Use of alternate formulations and techniques of immunosuppressant administration: Extended-release forms of tacrolimus**

Two extended-release formulations of tacrolimus (TAC) are now available: capsules (Advagraf XL<sup>®</sup> or Astagraf XL<sup>®</sup>) and tablets (Envarsus XR<sup>®</sup>). Products are not bioequivalent and dose conversions are recommended when switching between formulations.<sup>360</sup>

One study in 85 heart transplant recipients demonstrated comparable TAC exposure ( $AUC_{0-24}$  and  $C_{min}$ ) between the once-daily extended release, and twice daily capsules (162) although, one-third of patients required dose adjustments (25.9% requiring an increase), following changeover to extended-release TAC.<sup>144</sup>

Both extended-release preparations of TAC were compared with twice-daily immediate release TAC in an open-label, prospective, randomized, two-arm, three-period crossover study in 30 stable renal transplant recipients. Significantly higher exposure, prolonged time to peak concentration, and reduced fluctuation between peak and trough exposures, was found for extended-release TAC tablets. The authors recommended a 30% total daily dose reduction of 30% when converting from immediate release TAC capsules to extended release TAC tablets, and a 36% reduction when converting from extended release TAC capsules to extended release TAC tablets.<sup>360</sup>

Safety profiles appear to be comparable between the different TAC formulations, although long-term outcomes including efficacy data with extended-release TAC preparations remain to be determined.<sup>361, 362</sup>

Some studies suggest that once daily TAC administration may improve patient tolerability, and compliance, however further investigations are required to conclusively demonstrate this.<sup>363–366</sup>

There is very limited data on extended-release formulations in children after heart transplantation. One multiorgan trial randomizing 41 transplanted patients under 16 years to extended or immediate release TAC included 7 heart transplanted children, 3 of which were randomized to receive extended release.<sup>367</sup> Similar to a second European pediatric multicenter trial assessing conversion from immediate to extended release TAC including 2 heart, 48 kidney and 29 liver transplanted children, the main outcome was that extended release therapy was safe and well tolerated at 1 year follow-up, however, requiring frequent level monitoring and dose adaptation early postconversion. Both studies used Prograf® and Advagraf® and neither study was powered to identify subtle differences in safety or efficacy.<sup>367, 368</sup>

### ***Use of alternate formulations and techniques of immunosuppressant administration: Tacrolimus administration (sublingual, nasogastric, intravenous)***

During periods of limited or poor oral intake, administration of immunosuppressive agents using alternate routes or methods of administration may be required, as continuity of therapy is essential.

#### ***Oral liquid/nasogastric***

Liquid formulations facilitate drug administration via enteral feeding tubes, offer dosing flexibility particularly for pediatric patients, and provide a useful alternative for patients unable to swallow the oral tablets/capsules whole. Cyclosporine, mycophenolate mofetil, sirolimus, and the CS are commercially available as oral liquid preparations. Azathioprine and tacrolimus (TAC) may be extemporaneously compounded into an oral suspension.<sup>369–371</sup>

In addition to nasogastric administration, mycophenolate mofetil is suitable for jejunal administration, while azathioprine, sirolimus, and TAC are also suitable for both jejunal and duodenal administration.<sup>372</sup>

#### ***Sublingual***

For patients unable to take TAC capsules orally, or with poor absorption due to issues such as vomiting, gastroparesis, or ileus, sublingual administration may be a useful short-term alternative.

A standardized approach to dose conversion is still to be well established: 30 to 100% of the oral dose has been suggested when converting from oral to sublingual, depending on the organ transplanted, and the presence of concomitant interacting medications, with 50% being the most commonly used conversion.<sup>373–378</sup>

Administration techniques have also varied, with a method frequently used involving placing the contents of the capsule under the tongue. Health care providers

administering TAC with this method should wear at least two pairs of gloves, respiratory protection, and a non-permeable gown.<sup>373–375, 377–380</sup>

As studies are limited with this method of administration and long-term outcomes are not known, sublingual TAC should only be considered for short term use.<sup>381</sup>

#### ***Intravenous***

Intravenous (IV) immunosuppression may be indicated particularly when enteral administration is not feasible, and/or absorption is compromised which may lead to subtherapeutic levels. Commercial IV preparations are available for cyclosporin, tacrolimus, mycophenolate mofetil, azathioprine, and CS, and should be reserved when enteral options are unsuitable.

Anaphylactic reactions have been reported with intravenous formulations for the CNI's, associated with the castor oil derivative in TAC,<sup>382</sup> and the polyoxyethylated castor oil vehicle in CYA.<sup>383</sup>

Intravenous TAC is administered at approximately 10 to 33% of the total daily oral dose as a continuous infusion,<sup>382</sup> or twice daily as an intermittent infusion over 4 hours.<sup>384</sup> To avoid drug adsorption it should be administered using PVC-free syringes, bags, and tubing.<sup>382</sup>

CYA is administered intravenously at approximately one third of the total daily oral dose as an intermittent infusion over 2 to 6 hours twice daily, or as a continuous infusion. Due to the risk of phthalate stripping it should also be administered using PVC-free containers and giving sets.<sup>383</sup>

When administering TAC or CYA as a continuous infusion, drug concentrations measured will be at steady state (C<sub>ss</sub>) rather than trough (C<sub>0</sub>) levels.

#### ***Use of generic immunosuppressants***

Most of the innovator drugs used for maintenance immunosuppression in solid organ transplantation are now off patent, and in many countries, generic formulations are available, potentially increasing accessibility and affordability for both patient and health care providers.

Bioequivalence studies for generic drug approval are usually performed in healthy volunteers, and studies comparing efficacy outcomes following the switch from innovator to generic formulations in solid organ transplant recipients are often retrospective and comprised of small, stable cohorts.<sup>385–389</sup> However, the available evidence does not indicate an increased risk of rejection or incidence of adverse effects associated with their use, and comparable trough drug concentrations can be achieved, although dose changes in some patients may be required following the switch.<sup>385–389</sup>

Given that immunosuppressive drugs have a narrow therapeutic index, and appropriate dosing and monitoring of these agents is essential, patients should be educated to maintain the same brand of immunosuppressant wherever possible. Both patients and clinicians should be alert to when a brand substitution occurs, so that closer monitoring including drug levels, can be performed until a new steady state is established.



## Topic 3: Principles of Immunosuppression and Recommended Regimens

## 2010 Prior Guideline Recommendation

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

Class I, Level of Evidence: C

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

Class I, Level of Evidence: A

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

Class IIa, Level of Evidence: C

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

Class IIa, Level of Evidence: B

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

Class IIa, Level of Evidence: B

**New Recommendation****New Recommendation****New Recommendation****New Recommendation**

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.

Class IIa, Level of Evidence: B

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

Class IIa, Level of Evidence: C

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

Class IIa, Level of Evidence: C

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

Class IIa, Level of Evidence: C

## 2023 Guideline Update Recommendation

**Recommendation removed. Replaced with updated recommendations below.**

In adults, the use of statins after HT is recommended regardless of cholesterol levels. Due to pharmacologic interactions with CNI and risk for toxicity, statin doses should generally be lower than those recommended for hyperlipidemia.

**Class I, Level of Evidence: A**

Creatinine kinase and liver enzyme levels should be monitored in all patients receiving statins.

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

Continuing approval unchanged

Continuing approval unchanged

CNI free immunosuppression protocols are associated with an increased risk of rejection. CNI withdrawal should be especially avoided in the first 6 months after transplantation to reduce the risk of rejection and in recipients at high immunological risk.

**Class IIa, Level of evidence B**

Early introduction (within 6-12 months post transplant) of mTOR inhibitor may be associated with an attenuation of CAV. mTOR inhibitors when used within a CNI free regimen may provide long-term benefits on renal function. These benefits should be balanced with the individual risk of adverse events.

**Class IIa, Level of evidence B**

In CNI-free regimens, concomitant immunosuppression should be optimised including regular therapeutic drug monitoring to ensure adequate mTOR inhibitor trough concentrations are maintained.

**Class IIa, Level of evidence C**

In patients who do not tolerate other therapies such as MMF, EVL, or SRL, AZA may be considered for inclusion in the immunosuppressive regimen.

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

Continuing approval unchanged

In pediatric HT recipients the use of IL-2 antagonist or polyclonal antibody induction are beneficial over CS only induction and are also recommended when CS sparing or avoiding therapies applied. **Class IIa, Level of Evidence: B**

Routine use of statins is recommended for all pediatric transplant recipients older than 10 years, and younger patients with evidence of hyperlipidemia, CAV or following retransplantation. Due to pharmacologic interactions with CNI and risk for toxicity, statin doses should generally be lower than those recommended for hyperlipidemia. **Class IIa, Level of Evidence: C**

Continuing approval unchanged

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## Topic 3: Principles of Immunosuppression and Recommended Regimens

2010 Prior Guideline Recommendation	2023 Guideline Update Recommendation
CS avoidance, early CS weaning or very low dose maintenance CS therapy are all acceptable therapeutic approaches. Class IIa, Level of Evidence: B If used, CS weaning should be attempted if there are significant CS side effects and no recent rejection episodes (e.g., within 6 months). Class IIa, Level of Evidence: C	Continuing approval unchanged  If used, and there are no recent rejection episodes (e.g., within 6 months), CS weaning should be attempted to avoid significant CS side effects. <b>Class IIa, Level of Evidence: C</b>
Pediatric recipients with pre-formed alloantibodies and a positive donor-specific cross-match should receive induction therapy, and TAC-based “triple therapy” with CS and either MMF or an mTOR inhibitor. Class IIa, Level of Evidence: C	Pediatric recipients with pre-formed donor-specific alloantibodies and/or a positive crossmatch should receive induction therapy and TAC-based combination therapy. Pre-transplant desensitization including rituximab, IVIG and if needed bortezomib can be considered. Long-term therapy with TAC and an mTOR inhibitor is preferential. <b>Class IIa, Level of Evidence: C</b>
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. Class IIb, Level of Evidence: B	Continuing approval unchanged
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. Class IIb, Level of Evidence: C	Continuing approval unchanged
Most children should receive adjunctive therapy with an antimetabolite or a PSI. Class IIb, Level of Evidence: C	In the interest of graft longevity and diminishing effect on B-cell activation and proliferation, standard maintenance immune suppression in children should be a combination therapy including a CNI and an antiproliferative drug or mTOR inhibitor. <b>Class IIb, Level of Evidence: C</b>
If a child is intolerant of adjunctive therapy, the decision whether or not to replace it with another agent should be made following review of the patient’s rejection history and immunologic risk. TAC monotherapy is acceptable in patients with a benign rejection history. Class IIb, Level of Evidence: C	Monotherapy with a CNI should be the exception in pediatric transplant recipients if no adjunct therapy is tolerated and in absence of DSA and any rejection history. After PTLD and chemotherapy, transient monotherapy with a CNI or mTOR inhibitor have been successfully used <b>Class IIb, Level of Evidence: C</b>
For children diagnosed with CAV, the addition of an mTOR inhibitor should be strongly considered. Class IIb, Level of Evidence: C	For patients with presence of or at high risk of CAV (DSA, history of repeat acute rejection), a combination of CNI and mTOR inhibitor should be strongly considered. <b>Class IIa, Level of Evidence: B</b>
Routine use of immunosuppressive induction in all patients has not been shown to be superior to immunosuppressive regimens that do not employ such therapy. Class IIb, Level of Evidence: B	<b>In adults</b> , routine use of immunosuppressive induction has not been shown to be superior to immunosuppressive regimens that do not employ such therapy. <b>Class IIb, Level of Evidence: B</b>
Immunosuppressive induction with anti-thymocyte globulin (ATG) may be beneficial in patients at high risk for acute rejection. Class IIb, Level of Evidence: C	Continuing approval unchanged
Routine use of statins is recommended for adolescents and selected younger children with an increased risk of rejection or CAV. Class IIb, Level of Evidence: C	<b>Removed – included in recommendation above</b>
<b>New recommendation:</b>	Converting to mTOR inhibitor-based immunosuppression with reduction/discontinuation of CNI should be considered in patients with malignancies or PTLD as a therapeutic intervention to decrease the rate of recurrences. <b>Class IIb; Level of evidence C</b>
<b>New recommendation:</b>	At this time, routine rituximab induction cannot be recommended in non-sensitized cardiac transplant recipients. <b>Class III, Level of evidence: B</b>
<b>New recommendation:</b>	Agents such as belatacept and tocilizumab are evolving treatment options which may be considered as rescue therapy when standard approaches have failed, but at this time there is insufficient data to recommend their routine use. <b>Class IIb, Level of evidence: C</b>

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## Topic 3: Principles of Immunosuppression and Recommended Regimens

2010 Prior Guideline Recommendation	2023 Guideline Update Recommendation
<b>New recommendation:</b>	When switching between TAC formulations, a dose increase may be considered when converting from TAC immediate release to TAC extended-release capsules, and a dose decrease when converting from TAC capsules to TAC extended-release tablets. Close monitoring of TAC concentrations is essential during the changeover period between formulations, as further dose adjustments may be required to achieve similar TAC trough concentrations. <b>Class IIb, Level of Evidence: C</b>
<b>New recommendation:</b>	Alternative formulations such as liquid preparations of most oral IS agents can be useful particularly in pediatric patients or those with enteral feeding tubes. <b>Class IIb, level of evidence: C</b>
<b>New recommendation:</b>	Sublingual TAC may be considered an alternate administration method for short-term use. It is reasonable to use up to a 50% dose reduction of the current or anticipated oral dose when switching from oral to sublingual TAC in the absence of interacting medications. Following conversion, therapeutic drug monitoring must be continued, and doses adjusted to maintain adequate target levels. <b>Class IIb, Level of Evidence: C</b>
<b>New recommendation:</b>	If switching immunosuppressant brands, close surveillance to ensure adequate drug levels, continued efficacy, and for adverse effects, should be performed. Maintaining the same brand of immunosuppressant is preferable and repeated brand substitution should be avoided. <b>Class IIa, Level of evidence: C</b>

**Topic 4: Management of acute cellular rejection**

The incidence of treated rejection as reported to the International Thoracic Organ Transplant Registry of the International Society for Heart Lung and Lung Transplantation has continued to decline between 2004 and 2016. In the most recent cohort of patients transplanted between 2010 and 2016, 13% of patients experienced a treated rejection episode between the time of hospital discharge to their 1-year follow-up visit, compared to 24% of patients transplanted between 2004 and 2006.<sup>172</sup> The

management of acute cellular rejection has not changed appreciably since publication of the 2010 guidelines. The intensity of immunosuppression and the need for hospitalization are guided by both the endomyocardial biopsy histology grade and by symptoms of congestion (shortness of breath, abdominal bloating, orthopnea) or low cardiac output (fatigue, low blood pressures, and decreased urine output). Furthermore, the presence of LV or RV systolic dysfunction on echocardiography, even in the absence of symptoms, is typically treated as symptomatic rejection.<sup>390</sup>

## Topic 4: Management of Acute Cellular Rejection

## Recommendations for Treatment of Symptomatic Acute Cellular Rejection

2010 Prior Guideline Recommendation	2023 Guideline Update Recommendation
An EMB should be performed as early as possible if there is suspicion of symptomatic acute heart allograft rejection. Class I, Level of Evidence: C	Continuing approval without change.
The HT recipient with symptomatic acute cellular rejection should be hospitalized. Patients with hemodynamic compromise should be treated in the ICU. Class I, Level of Evidence: C	The HT recipient with symptomatic acute cellular rejection should be hospitalized. Patients with hemodynamic compromise (hypotension, low cardiac output, or marked elevation of pulmonary capillary wedge pressure) should be treated in the ICU, or an intermediate-care unit with the ability to perform continuous hemodynamic monitoring and administer inotropes. <b>Class I, Level of Evidence: C</b>

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*(Continued)***Topic 4: Management of Acute Cellular Rejection****Recommendations for Treatment of Symptomatic Acute Cellular Rejection**

2010 Prior Guideline Recommendation	2023 Guideline Update Recommendation
High-dose IV CS should be first-line therapy for symptomatic acute cellular rejection irrespective of ISHLT EMB grade (1R, 2R, or 3R). Class I, Level of Evidence: C	Continuing approval without change.
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. Class I, Level of Evidence: C	Continuing approval without change.
IV inotropes and vasopressors should be used as necessary to maintain adequate CO and systemic blood pressure until recovery of heart allograft function occurs. Class I, Level of Evidence: C	Continuing approval without change.
Antimicrobial prophylaxis against opportunistic infections should be administered when high-dose CS and/or cytolytic therapy are used for the treatment of rejection. Class I, Level of Evidence: C	Continuing approval without change.
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). Class I, Level of Evidence: C	Continuing approval without change.
Follow-up EMB should be done 1 to 2 weeks after initiation of therapy for acute cellular rejection. Class I, Level of Evidence: C	Follow-up EMB should be performed 2 to 4 weeks after initiation of therapy for acute cellular rejection, unless there is a compelling indication for earlier histologic evaluation. <b>Class I, Level of Evidence: C</b>
In a patient with low-grade acute cellular rejection and hemodynamic compromise, the possibility of AMR should also be entertained (see AMR section). Class I, Level of Evidence: C	In a patient with low-grade acute cellular rejection and hemodynamic compromise, the possibility of AMR (see AMR section) and/or CAV should also be entertained. <b>Class I, Level of Evidence: C</b>
IL-2 receptor blockers should not be used to reverse acute cellular rejection. Class I, Level of Evidence: C	Continuing approval without change.

**Recommendations for the Treatment of Asymptomatic Acute Cellular Rejection**

2010 Prior Guideline Recommendation	2023 Guideline Update Recommendation
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. Class I, Level of Evidence: C	Continuing approval without change.
High dose IV CS should be given for asymptomatic severe (ISHLT 3R) acute cellular rejection. Class I, Level of Evidence: C	Continuing approval without change.
Asymptomatic moderate acute cellular rejection (ISHLT 2R) can be treated with either IV or oral CS. Class I, Level of Evidence: C	Continuing approval without change.
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. Class I, Level of Evidence: C	Continuing approval without change.

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*(Continued)***Recommendations for the Treatment of Asymptomatic Acute Cellular Rejection**

2010 Prior Guideline Recommendation	2023 Guideline Update Recommendation
Cytolytic immunosuppressive therapy can be considered if there is no histological resolution of rejection on the follow-up EMB. Class IIa, Level of Evidence: C	Continuing approval without change.
Antimicrobial prophylaxis against opportunistic infections should be administered when high-dose CS and/or cytolytic therapy are used for treatment of rejection. Class I, Level of Evidence: C	Continuing approval without change.
The performance of a follow-up EMB should be considered 2 to 4 weeks after initiation of therapy of asymptomatic moderate or severe acute cellular rejection. Class IIa, Level of Evidence: C	Continuing approval without change.
Asymptomatic mild cellular rejection (ISHLT 1R) does not require treatment in the vast majority of cases. Class IIa, Level of Evidence: C	Asymptomatic mild cellular rejection (ISHLT 1R) does not require treatment in most cases, but maintenance doses of immunosuppressive agents should be adjusted to ensure levels are within the recommended therapeutic range. <b>Class IIa, Level of Evidence: C</b>
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. Class IIb, Level of Evidence: C	Asymptomatic moderate cellular rejection (ISHLT 2R) occurring later than 12 months after HT may not require treatment, but maintenance doses of immunosuppressive agents should be adjusted to ensure levels are within the recommended therapeutic range, and conversion to a different immunosuppressive maintenance regimen should be considered. Close surveillance (clinical, echocardiographic, and follow-up EMB) is strongly suggested if no treatment is administered in this setting <b>Class IIb, Level of Evidence: C</b>

**Recommendations for Treatment of Recurrent or Resistant Acute Cellular Rejection**

2010 Prior Guideline Recommendation	2023 Guideline Update Recommendation
For recurrent or CS-resistant acute cellular rejection, cytolytic immunosuppressive therapy with antithymocyte antibodies should be considered. Class I, Level of Evidence: C	Continuing approval without change.
Maintenance immunosuppression should be re-evaluated in patients with recurrent/resistant HT rejection (see above). Class I, Level of Evidence: C	Continuing approval without change.
Frequent surveillance of heart allograft function (e.g., by echocardiography) is recommended in patients with recurrent/resistant rejection, even if persistently asymptomatic. Class I, Level of Evidence: C	Continuing approval without change.
Additional approaches that can be considered for recurrent or resistant acute cellular rejection include methotrexate pulse therapy, photopheresis and total lymphoid irradiation. Class IIb, Level of Evidence: B	Recurrent or resistant acute cellular rejection that occurs after treatment with CS and cytolytic immunosuppressive therapy and optimization of the patient's maintenance immunosuppressive regimen can be treated with photopheresis or total lymphoid irradiation <b>Class IIa, Level of Evidence: B</b>
Evaluation of EMB specimens for concomitant 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. Class IIb, Level of Evidence: C	Evaluation of EMB specimens for concomitant 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 recommended. <b>Class I, Level of Evidence: C</b>

## Topic 5: Treatment of hyperacute and antibody-mediated rejection

The importance of B-cell immunity and donor directed antibodies has increasingly been recognized as a highly relevant concern in heart and other solid organ transplantation.<sup>391</sup> While higher level detectable antibodies against HLA epitopes represent the end-product of a mature adaptive immune response to these antigens, the mechanisms of damage to the graft encompass multiple levels and direct involvement of the B-cells as antigen presenting cells and provider of immune memory.<sup>392</sup> The harmful effect of antibodies can be directly mediated via complement activation but also includes effects of opsonization and chemotaxis resulting in invasion of immune cells into the coronary-vascular wall of the graft, resulting in subsequent antigen presentation with enhanced T-cell response, endothelial inflammation and proliferation and fibrosis ultimately protruding into the vascular lumen and reducing downstream perfusion reflecting CAV.<sup>393</sup> The different pathways involved depend on the antibody specificity, affinity and biological activity and these explain the variability in presentation of AMR from rare hyperacute to variable intensity of acute rejection and finally asymptomatic or subclinical phenotypes.<sup>394, 395</sup> Generally, class I HLA antigens are expressed on every nucleated cell in the body including the graft resulting in a higher likelihood of directly visible graft impairment. Class II is only expressed on antigen presenting cells, which includes activated coronary endothelium, commonly resulting in a more subtle chronic clinical presentation, represented by allograft vasculopathy in the heart in adults and children.<sup>230, 262, 396, 232</sup>

Post-transplant monitoring for DSA should be performed at 1-, 3-, 6-, and 12 months postoperatively.<sup>177</sup> Patients at low risk should be monitored annually for DSA after the first year. Sensitized patients should be monitored more frequently. Although the development of de novo DSA confers risk for allograft rejection, development of CAV, and increased mortality, there is no consensus on the management of DSA in patients who are doing well with no evidence of allograft dysfunction.

### Antibody mediated rejection

In keeping with the variability of clinical presentation of AMR there is also a wide range of therapeutic options with currently no unanimous agreement on the ideal approach, combination and intensity of treatment.<sup>177</sup> The intensity of therapeutic response can be guided by the acuity and context of the clinical presentation from asymptomatic new DSA detected in routine surveillance over progressive CAV to acute and hyperacute rejection pictures. Therapies can target antibody generation, physically remove antibodies from plasma or reduce downstream effects of graft injury. The management of AMR starts with its prevention. Exposure of prospective HT recipients to alloantigens should be minimized; nonessential blood product transfusions should be avoided and when transfusion is needed, leukocyte-depleted products should be used. A sensitizing

effect of VAD use was also consistently found although the extent and impact on post-transplant outcomes appears variable.<sup>397</sup>

*Pathological diagnosis of AMR.* In 2013, the ISHLT published a consensus paper on the diagnosis and classification of AMR in pathologic specimens.<sup>398</sup> It incorporates histopathologic and immunopathologic findings, reported as pathologic or pAMR according to an ISHLT pAMR format. (See Table with related categories.) The histopathologic criteria are evaluated on Haematoxylin Eosin staining characterized as intravascular activated mononuclear cells, notably intravascular macrophage accumulation in capillaries and venules that distend and fill vascular lumens and endothelial cells swellings that appear to narrow or occlude the lumens. Severe antibody mediated rejection is reported in the presence of hemorrhage, interstitial edema, myocyte necrosis, capillary fragmentation, mixed inflammatory infiltrates, endothelial cell pyknosis, and/or karyorrhexis.

The immune-pathologic features are evaluated with a panel of antibodies to identify the intravascular infiltration of macrophages and markers of antibody deposition or complement activation, both on paraffin sections (C4d and CD 68) or on immunofluorescence sections (C4d, C3d, HLA-DR) and scored according to intensity and distribution.<sup>398</sup>

The categories for the reporting of AMR are as follows:

- **pAMR 0—negative for pathologic AMR:** histopathologic and immunopathologic studies are both negative.
- **pAMR 1 (H+)—histopathologic AMR alone:** histopathologic findings present **and** immunopathologic findings negative.
- **pAMR 1 (I+)—immunopathologic AMR alone:** histopathologic findings negative **and** immunopathologic findings positive; that is, CD68+ and/or C4d+ for IHC and C4d+ with or without C3d+ for IF.
- **pAMR 2—pathologic AMR:** histopathologic **and** immunopathologic findings are both present.
- **pAMR 3—severe pathologic AMR:** interstitial hemorrhage, capillary fragmentation, mixed inflammatory infiltrates, endothelial cell pyknosis, and/or karyorrhexis and marked edema **and** immunopathologic findings are present.

The role of non-HLA antibodies in AMR continues to evolve. For example, the presence of angiotensin receptor-1 (AT1R) antibodies in conjunction with HLA-DSA appears to be a negative prognostic marker in heart transplantation, however, their independent relevance remains unclear.<sup>399</sup>

### Hyperacute form of antibody mediated rejection

The term hyperacute rejection is used when immune-mediated acute graft dysfunction manifests within minutes or hours after HT. The severe graft injury results from high titers of antibodies directed against donor antigens which are present in the recipient's serum at the time of transplantation and typically results in cardiogenic shock.

Hyperacute rejection is rare, as sera of transplant candidates are routinely screened for the presence of anti-HLA antibodies.

Treatment, which must be initiated immediately, may include temporary MCS, IV inotropes and vasopressors, CS, plasmapheresis, high dose IVIG, cytolytic agents, and eculizumab. The baseline maintenance immune suppression can be intensified by targeting higher trough level ranges and should at minimum include a CNI (CYA or tacrolimus) and metabolic cycle inhibitors (MMF or cyclophosphamide) or mTOR inhibitor (Sirolimus or Everolimus). Temporary biventricular support should be considered early as the full effect of the immunosuppressive therapies may not occur for hours or days. If these measures do not sufficiently improve graft function, consideration should be given to durable MCS which may require biventricular support (bilateral VADs or TAH) to facilitate further immunotherapy.<sup>400</sup> Urgent retransplantation is generally not an option in the setting of immune activation and it has been consistently associated with a high mortality risk.<sup>397, 401, 402</sup>

*Acute antibody mediated rejection.* Approach to the management of acute AMR occurring outside the immediate transplant period may include similar therapeutic options as in hyperacute rejection (Table 9). Initial therapy, especially when hemodynamic alterations are present may require inotropic or mechanical support and medical therapy and should include high-dose IV CS (methylprednisolone, 500-1000 mg daily or 10mg/kg/day for children given for 3 consecutive days). Cytolytic therapy with polyclonal anti-thymocyte globulin can be used as escalation due to lack of response or in very severe presentation.<sup>397</sup> Successful use of IL2-receptor antagonists has not been described for AMR.

Plasmapheresis, immune apheresis (immunoadsorption) and IV immunoglobulin decrease the impact of circulating antibodies.<sup>397</sup> Following antibody removal, IV immunoglobulin provides further immunomodulatory effects (see below) and replacement may decrease risk of infection.

Plasmapheresis removes alloantibodies from the recipient's plasma. There is no consensus on the number or frequency of plasmapheresis sessions; common protocols range from 1 to 5 times per week for 1 to 4 weeks (Table 10).

Tables 7, 8 and 9

Immune apheresis (immunoadsorption) can also be used to remove circulating antibodies. As compared to plasmapheresis, it is less efficient in removing circulating cytokines but is more specific in removal of antibodies and poses significantly less hemodynamic stress. Immune apheresis is less widely available than plasmapheresis, and therefore, is less commonly used.<sup>397</sup>

A recently developed method uses cleavage of IgG with a streptococcal endopeptidase (immunoglobulin-depleting enzyme of *Streptococcus pyogenes*, IDES, imlifidase) to separate the Fc and Fab fragments of IgG, thus reducing complement activation in and any type of Fc-mediated antibody effect. It has been found effective to deplete HLA antibodies in a pilot trial in kidney transplantation however, data in cardiac transplantation and long-term impact assessment are currently missing.<sup>404, 405</sup>

Administration of IV immunoglobulin at various doses and intervals is used in the treatment of AMR (Table 10). Immunoglobulin therapy is believed to decrease production of antibodies and to modify the immune reactivity of antibodies that are already in circulation as well as blocking receptors for the Fc antibody compartment, thereby reducing downstream effects of DSA. Additionally, IV immunoglobulin provides protection from infections in the context of B-cell and/or plasma cell depletion performed for AMR treatment. Cyclophosphamide had been used as a B-cell targeting agent, but its role with current immunosuppressive protocols is unclear and the adverse effects may outweigh the benefits in a transplant setting.

The role of rituximab, an antibody directed against the CD 20 antigen expressed on B-lymphocytes, is being evaluated.<sup>397</sup> Table 10 lists rituximab dosing that has been most frequently used in treatment of AMR. Rituximab was found to effectively deplete B-cells and memory B-cells, however,

**Table 6** Significant Differences in Primary Endpoints Between Study Groups From Major Clinical Trials Since 2010

Author (year)	Study	No.	Follow-up	Survival	Rejection	CAV by IVUS
Barten (2019)	MANDELA: EVL/redCNI vs CNI-free	162	1 year	NS	CNI-free = more rejection	NS
Potena (2018)	EVERHEART: Immediate ( $\leq 144$ h) (EVL-I) vs delayed (4-6 weeks post-HTx) (EVL-D) EVL initiation	181	6 months	NS	EVL-I = higher incidence BPAR $\geq 2R$ (but not SS)	NS
Arora (2015) Andreassen (2016)	SCHEDULE: redCYA/EVL & CNI withdrawal at 7-11 weeks vs CYA+ MMF	115	1-3 years	NS	EVL group = more rejection	EVL group = less CAV
Eisen (2013)	CRAD 2310: redCyA/EVL 1.5mg vs redCyA/EVL 3mg (dc) vs CYA/MMF	721	12-24 months	NS	No significant differences between groups	EVL/redCYA group = less CAV

**Table 7** Significant Differences in Adverse Events From the Major Clinical Trials Since 2010

Author (year)	Study	No.	Renal function	Infections	Cholesterol & triglycerides	Hypertension
Barten (2019)	MANDELA: EVL/redCNI vs CNI-free	162	CNI-free = better renal function	CNI-free = less CMV (? SS, no <i>p</i> -value)	-	EVL/redCNI = more hypertension (? SS, no <i>p</i> -value)
Potena (2018)	EVERHEART: Immediate ( $\leq 144$ h) (EVL-I) vs delayed (4-6 weeks post-HTx) (EVL-D) EVL initiation	181	comparable between both groups	EVL-I = lower risk CMV	No significant differences between groups	No significant differences between groups
Arora (2015) Andreassen (2016)	SCHEDULE: redCYA/EVL & CNI withdrawal at 7–11 weeks vs CYA+ MMF	115	EVL = better renal function	No significant differences between groups	NS	No significant differences between groups
Eisen (2013)	CRAD 2310: redCyA/EVL 1.5mg vs redCyA/EVL 3mg (dc) vs CYA/MMF	721	EVL/redCYA = inferior for renal function but comparable if predefined redCYA level achieved	EVL/redCYA = less CMV	EVL/redCYA = higher total cholesterol & HDL = higher LDL & TG at 1 year only	No significant differences between groups

since plasma cells as actively antibody secreting cells do not express CD20 they are not depleted by rituximab. Accordingly, a therapeutic effect can only be observed after these plasma cells naturally decline which in the context of AMR may take weeks to months. A direct benefit of B-cell

depletion may arise from their role as antigen presenting cell as described in autoimmune diseases.<sup>395</sup> In most patients a single dose of rituximab at 375 mg/msq depletes B-cells for 6 to 12 months below detection limits in peripheral blood, however, a 4 dose regimen over 4 weeks has

**Table 8** Significant Differences in Adverse Events From the Major Clinical Trials Since 2010

Author (year)	Study	No.	Hematologic	GI disorders	Other
Barten (2019)	MANDELA: EVL/redCNI vs CNI-free	162	No significant differences between groups	EVL/redCNI = more diarrhoea & nausea (? SS, no <i>p</i> -value)	-
Potena (2018)	EVERHEART: Immediate ( $\leq 144$ h) (EVL-I) vs delayed (4-6 weeks post-HTx) (EVL-D) EVL initiation	181	No significant differences between groups	NS	EVL-I = more pericardial effusion = more AEs = more discontinuations due to AEs & serious AEs EVL-I = 48% nonsignificant increase in the relative risk of incidence of the primary endpoint (postoperative wound healing delays, pericardial effusion, pleural effusion needing drainage and acute renal insufficiency events)
Arora (2015) Andreassen (2016)	SCHEDULE: redCYA/EVL & CNI withdrawal at 7–11 weeks vs CYA+ MMF	115	No significant differences between groups	-	No significant differences between groups for surgical events or wound complications
Eisen (2013)	CRAD 2310: redCyA/EVL 1.5mg vs redCyA/EVL 3mg (dc) vs CYA/MMF	721	EVL/redCYA = more anemia	-	EVL 3mg/redCYA arm = enrolment dc due to higher early mortality EVL/redCYA = more pericardial effusion

AE, adverse event; dc, discontinued; NS, not stated; SS, statistically significant.



**Table 9** Desensitization and AMR and Therapies

Therapy <sup>403</sup>	Mechanism of action	Immune effects	Major adverse effects
Alemtuzumab	CD52 monoclonal antibody	Depletes circulating lymphocytes, macrophages, and monocytes	Leukopenia, thrombocytopenia, infusion related reactions
Bortezomib	Proteasome inhibitor	Depletes plasma cells	Peripheral neuropathy, thrombocytopenia, neutropenia
Carfilzomib	Proteasome inhibitor	Depletes plasma cells	AKI, thrombocytopenia, cardiotoxicity
Eculizumab	Complement C5 inhibitor	Inhibits formation of terminal complement C5b-9	Meningococcal infection (Vaccination recommended)
Intravenous immunoglobulin	Immunomodulatory effects	Neutralize circulating antibody, inhibit complement, inhibit B cells	Infusion-related reactions, hemolysis, interference with antibody assays
PIasmapheresis	Extracorporeal plasma antibody filtration	Removes circulating immunoglobulins	Access and line related complications, coagulopathy
Rituximab	CD20 monoclonal antibody	Depletes circulating B cells	Infusion-related reactions
Splenectomy	Removal of secondary lymphoid organ	Removes major source of lymphocytes	Encapsulated bacterial infections

been suggested to enhance an effect on B-cells in lymph nodes.<sup>406</sup>

Plasma cells can directly be depleted using proteasome inhibitors (bortezomib, carfilzomib) resulting in fast and effective antibody reduction when used in combination with steroids, rituximab and antibody removal as shown in larger adult kidney transplant and small pediatric heart transplant trials, associated with improved graft function in the context of acute AMR. Whether there is an effect on late AMR and CAV remains unclear, but renal transplant data suggest less impact. Polyclonal and monoclonal antilymphocytic antibodies, IV immunoglobulin or rituximab should not be given shortly before plasmapheresis or immune apheresis, as they are removed by this process.<sup>347, 407–409</sup>

When AMR is complicated by hemodynamic compromise, IV inotropic agents and vasopressors and at times MCS may be required to maintain adequate organ perfusion until heart allograft function is sufficiently improved. Systemic anticoagulation may be considered during an episode of AMR. This is aimed to prevent microvascular thrombosis of the allograft coronary vasculature associated with AMR.<sup>410</sup>

Limited recent data suggest that use of bortezomib, eculizumab, and total lymphoid irradiation may be effective

for refractory AMR with hemodynamic compromise that is resistant to plasmapheresis and antithymocyte globulin.<sup>411</sup>

While data on the differential effects of various maintenance immunosuppressive regimens on the prevention of recurrence of AMR are scarce, modifications of baseline immunosuppression seem reasonable. In a randomized trial the use of tacrolimus with sirolimus was associated with significantly lower treated rejection compared with tacrolimus or cyclosporine with MMF. Although not directly examined, the rate of any-treated rejection in this trial exceeded the rate of biopsy-proven cellular rejection in the primary end point by 10% to 20%, depending on the arm, implying that there was a significant presence of AMR. Patients with history of treated or recurrent AMR may be considered for adjustment of maintenance therapy.<sup>297</sup> Other options include:

- Increase of the dose and target trough levels of current immunosuppressive medications.
- Addition of an agent. For example, restarting CS, adding an mTOR inhibitor (mTORi), or adding cyclophosphamide.
- Conversion to a different maintenance regimen. Conversion from CYA to TAC, or from AZA to MMF or mTORi or MMF to mTORi.<sup>397</sup>

**Table 10** 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
IV immunoglobulin	100-2000 mg/kg	Once weekly	2-4 weeks
		Low dose 1-3 times per week, often given after each plasmapheresis	1-4 weeks
Rituximab	375 mg/m <sup>2</sup>	Once weekly	1-4 weeks
IV Ig, intravenous immunoglobulin.			

Splenectomy has been used to treat recurrent AMR in kidney transplant recipients but data regarding its role in HT are lacking.

Follow-up EMB should be performed 2 to 4 weeks after initiation of therapy for acute AMR. Microarray molecular diagnostic analysis (Molecular Microscope<sup>®</sup>) of EMB may provide supplemental data with regard to response to therapy. Measurement of serum donor-specific antibodies and changes in their levels in response to therapy should be considered.<sup>412</sup>

*Asymptomatic antibody mediated rejection.* Histological findings of AMR may be present without graft dysfunction. Some data suggest that AMR, even without heart allograft dysfunction, may lead to increased incidence of CAV and cardiovascular mortality.<sup>413, 414</sup> It is unclear whether or which therapies improve the prognosis of this condition. Currently, when asymptomatic AMR is diagnosed, it is wise to assure that baseline immunosuppression is adequate with consideration for resumption of CS, conversion of antimetabolite to mTORi and the patient is closely monitored.

*Mixed rejection.* The term mixed rejection has been used in circumstances where EMB reveals abnormalities consistent with both cellular rejection and AMR. When hemodynamic compromise is present, aggressive therapy with high-dose IV CS, and cytolytic therapy is appropriate. Additional therapies directed at AMR should be considered. In mild forms of mixed rejection without significant symptoms, therapy should in general follow the algorithm for cellular rejection with consideration for additional IVIG.

### **Additional specific considerations for pediatric recipients**

The principles of acute rejection therapy in children are comparable to those in adults. In children deterioration is often rapid when any degree of graft dysfunction is present and close monitoring is required. With echocardiographic evidence of severe graft dysfunction, it is prudent to begin inotropes, even if the child does not appear acutely ill. Infants and small children with hemodynamic compromise are sometimes treated empirically without EMB due to the risks of precipitating clinical deterioration with the anesthesia required to perform the procedure. Since the most severe forms of rejection are sometimes reversible, MCS can be instituted if graft failure occurs, however, especially in the context of CAV the success of longer-term MCS support is limited. In smaller children the use of antibody removal strategies may be limited by the need for large lumen intravascular access and intolerance of the required blood volume shifts for plasmapheresis. Therefore, other strategies (B-cell and plasma cell depletion, IVIG) may be preferred in these patients.

An additional aspect in young children is the option of ABO incompatible transplantation which is now offered to up to 70% and performed in up to 40% of children

<2 years and adds an additional level of mismatch and donor directed antibodies.<sup>191</sup> Most current pediatric organ transplant policies limits ABO incompatible transplant to children <2 years of age with anti A/B titers of  $\leq 1:32$  and includes prophylactic intraoperative antibody removal. In this setting, isolated isohemagglutinin related AMR has not been observed, but has been detected in conjunction with HLA-mediated AMR.<sup>190, 195, 286</sup> Isohemagglutinin titers towards the donor blood group remain absent or severely suppressed in the majority of recipients for many years.<sup>190, 415</sup> Interestingly, post-transplant de novo HLA-DSA were found to be less prevalent after ABO incompatible than ABO compatible transplantation in children transplanted <2 years of age.<sup>416, 417</sup> Accordingly, no higher vigilance except for monitoring of donor-type isohemagglutinin titers for AMR is required in ABO incompatible transplant patients.

Many children with congenital heart disease become highly sensitized due to prior surgeries including the use of human tissue. Given the limited availability of pediatric organs these patients are unlikely to receive a donor organ with a negative donor-specific crossmatch. Selected patients with very short life expectancy are being transplanted with organs for which the donor-specific cross-match will be positive and in these patients there may be an overall survival benefit as compared to waiting for a negative crossmatch.<sup>397, 418</sup> When transplanting though a positive cross match prophylactic intraoperative and early postoperative plasma exchange or plasmapheresis are necessary. The recipients should be managed with polyclonal antibody induction therapy, and TAC-based immunosuppression in combination with a CS and MMF which may later be replaced with an mTOR inhibitor. Duration of plasmapheresis treatment depends upon various factors including pre-transplant antibody concentrations. A process of 'accommodation' to the allograft may occur in patients allowing the patient to overcome recover from the acute rejection effects, however, a higher incidence of CAV is highly associated with a history of AMR in children.<sup>230, 232, 397</sup> Early graft dysfunction should lead to reintroduction of plasmapheresis if previously discontinued. The role of rituximab, proteasome inhibitors and newer monoclonal antibodies directed at plasma cells is not well established. During longer term follow-up, this population may be at high risk for the development of CAV. A multicenter observational study of late outcomes of children transplanted across a positive crossmatch has been ongoing (NCT0275278), however, detailed outcomes are not yet reported.

Fortunately, hyperacute rejection triggered by preformed antibodies against ABO or HLA antigens occurring within minutes or hours after HT remains rare, due to better understanding of the role of preformed antibodies, better detection techniques, improved donor organ selection and intensified immune manipulation in sensitized patients. More commonly AMR occurs in the first weeks and months after HT, although late subclinical AMR is increasingly recognized and associated with increased development of CAV and mortality in adults and children.<sup>230, 262, 396</sup>

## Topic 5 Treatment of Hyperacute and Antibody-Mediated Rejection

### Recommendations for the Treatment of Hyperacute Rejection

#### 2010 Prior Guideline Recommendation

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 Ig; (4) cytolytic immunosuppressive therapy; (5) IV CNI (CYA, TAC) and metabolic cycle inhibitors (MMF); (6) IV inotropes and vasopressors; (7) mechanical circulatory support.

Class I, Level of Evidence: C.

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.

Class IIb, Level of Evidence C

#### 2023 Guideline Update Recommendation

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) MCS. (2) high-dose IV CS; (3) plasmapheresis; (4) IVIG; (5) Rituximab (6) cytolytic immunosuppressive therapy; (7) Eculizumab (8) IV CNI (CYA, TAC) with increased target levels and metabolic cycle inhibitors (MMF); (9) IV inotropes and vasopressors; (10) heparin

**Class I, Level of Evidence: C.**

Placement of MCS may be considered as a bridge to re-transplantation. Urgent retransplantation may be considered and is associated with increased mortality. Existing DSA epitopes should be avoided on the retransplant organ

**Class IIb, Level of Evidence C**

### Recommendations for Treatment of Acute Antibody Mediated Rejection

#### 2010 Prior Guideline Recommendation

The following treatments can be used to disrupt the immune-mediated injury of the heart allograft in AMR:

(1) high-dose IV CS; (2) cytolytic immunosuppressive therapy.

Class IIa, Level of Evidence C

Conversion to a different maintenance regimen. Conversion from CYA to TAC, or from AZA to MMF.

Class IIa Level of Evidence C

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

Class IIa, Level of Evidence C

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

Class IIa, Level of Evidence C

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

Class IIa Level of Evidence: C.

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

Class IIa, Level of Evidence C

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

Class IIa, Level of Evidence C

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).

Class IIa, Level of Evidence LOE C

#### 2023 Guideline Update Recommendation

The following treatments can be used to disrupt the immune-mediated injury of the heart allograft in AMR:

(1) high-dose IV CS; (2) cytolytic immunosuppressive therapy. (3) Rituximab (4) Bortezomib or carfilzomib (5) Eculizumab

**Class IIa, Level of Evidence C**

Intensify the maintenance regimen, possibly including conversion from CYA to TAC, or from AZA to MMF, replacement of the AZA/MMF with a mTORi, increasing target trough levels, and/or addition of low-dose CS and additional immunological monitoring is recommended.

**Class IIa Level of Evidence C**

Continuing approval without change

Continuing approval without change

When AMR is suspected EMB examination should include AMR pathology assessment and classification according to the ISHLT grading consensus.

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

When AMR is suspected recipient serum should be evaluated for the presence, quantity and specificity of anti-donor (HLA) antibodies. Serum samples should be drawn before initiation of therapy to avoid assay interference from therapeutic agents.

**Class IIa, Level of Evidence C**

Continue approval without change

Adjustment of maintenance immunosuppressive therapy may be considered. This can include increase in the dose of current immunosuppressive agent(s), and/or conversion to a different maintenance regimen including conversion from CYA to TAC, or from AZA to MMF or mTORi or MMF to mTORi.

**Class IIa, Level of Evidence B**

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## Recommendations for Treatment of Acute Antibody Mediated Rejection

2010 Prior Guideline Recommendation	2023 Guideline Update Recommendation
Systemic anticoagulation may decrease intravascular thrombosis in the heart allograft. Emergent retransplantation may be considered if the above measures do not restore acceptable heart allograft function. Class III, Level of Evidence: C.	Continuing approval without change  Emergent MCS may be considered as a bridge to retransplantation if the above measures do not restore acceptable heart allograft function. Emergent retransplantation following acute rejection is associated with unfavorable outcomes. <b>Class III, Level of Evidence: C.</b>

**Topic 6: Management of late acute rejection**

Late rejection refers to rejection episodes that occur after the first post-transplant year. Risk factors for late rejection include younger recipient age, prior history of acute rejection episodes or episodes occurring > 6 months after transplantation, African American ethnicity, presence of HLA donor-specific antibodies, donor and recipient sex mismatch, calcineurin-inhibitor (CNI) reduced or free immunosuppression, and a history of medication non-adherence.<sup>324, 419–422</sup>

Additionally, adolescent solid organ transplant recipients, comprising late teenage to young adulthood (14-27 years), are at particular risk for nonadherence and increased rates of late acute rejection, development of de novo HLA-DSA and graft loss.<sup>423, 424</sup> Lifestyle changes, progressive independence from parent care and supervision, the need to take more individual responsibility, behavioral challenges, and mental health struggles coincide with transition of clinical care from pediatric to adult transplant teams.<sup>425–427</sup> Therefore, in this age group, careful assessment of

adherence, mental health, and psychosocial/behavioral issues is of particular importance when detecting late rejection. Whether structured programs when transitioning from pediatric to adult care can ameliorate the risk is the subject of multiple studies.<sup>428–430</sup>

Observational studies in the last decade have identified antibody-mediated rejection (AMR) as an important cause of late rejection, accelerated CAV, and graft failure.<sup>396, 431, 432</sup> Therefore, patients presenting with signs or symptoms of graft dysfunction late after HT should undergo an evaluation for AMR with EMB and immunostaining for complement activation or antibody binding before steroid treatment and should be tested for the presence of circulating HLA donor-specific antibodies.<sup>176, 433</sup> In addition to AMR, CAV remains a frequent cause of late graft dysfunction and should be considered in the differential diagnosis.<sup>434</sup> CAV should be excluded by angiography and intravascular ultrasound (IVUS) or optical coherence tomography (OCT), as imaging modalities for vessel wall changes seem to be useful in pediatric and adult patients and may detect changes prior angiographic presentation.<sup>435, 436</sup>

## Topic 6: Recommendation for the Management of Late Acute Rejection

## Recommendation for the Management of Late Acute Rejection

2010 Prior Guideline Recommendation	2023 Guideline Update Recommendation
Maintenance immunosuppression and the intensity of clinical follow-up should be re-evaluated after symptomatic or asymptomatic late acute heart allograft rejection. Class I, Level of Evidence: C After the first year, EMB surveillance (e.g., 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 the risk of death in African American recipients. Class IIa, Level of Evidence: C	Continuing approval without change.  After the first year, continued rejection surveillance (using a combination of noninvasive methods, GEP or EMB) is reasonable in patients at higher risk for late acute rejection. Risk factors for rejection include younger recipient age, prior history of acute rejection episodes, presence of donor-specific-antibodies, recipient female gender, rejection events occurring >6 months after transplantation, CNI-reduced or -free immunosuppression, and a history of medication of non-compliance. The optimal frequency and duration of rejection surveillance have not been defined. <b>Class IIa, Level of Evidence: C</b>
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. Class IIa, Level of Evidence: C	Continuing approval without change.

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*(Continued)***Topic 6: Recommendation for the Management of Late Acute Rejection****Recommendation for the Management of Late Acute Rejection****2010 Prior Guideline Recommendation**

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.

Class IIa, Level of Evidence: C

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.

Class IIa, Level of Evidence: C

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.

Class IIa, Level of Evidence: C

**New recommendation****New recommendation****2023 Guideline Update Recommendation**

Continuing approval without change.

In pediatric and adult HT recipients, CAV should be considered as differential diagnosis of late symptomatic or asymptomatic rejection when heart allograft dysfunction is present. Coronary angiography and IVUS or optical coherence tomography [OCT] should be considered in these patients during long-term follow up.

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

In pediatric and adult 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 with IVUS or OCT, when available, is recommended.

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

Antibody mediated rejection is more commonly identified in late acute rejection compared to acute cellular rejection and should be considered in the differential diagnosis of HT recipients presenting with signs or symptoms of heart allograft dysfunction. EMB with ISHLT immunopathologic evaluation, as well as measurement of circulating HLA donor-specific-antibodies should be obtained before initiating treatment.

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

Careful assessment of adherence to medications, co-medications or supplements interfering with IS and triggering events (infections, GI disorders) is recommended in any case of late rejection in adult and pediatric patients, but especially in high-risk groups for non-adherence such as adolescents, young adults, and patients with a history of mental illness or non-adherence. **Class IIa, Level of Evidence: B**

**Task Force 3: Long-term care of heart transplant recipients: management of complications**

Chair: Kyung-Hee Kim

Co-Chair: Shelly Miyamoto

Contributing Writers: Sharon Chih, Kevin Daly, Paolo Grossi, Doug Jennings, In-cheol Kim, Sern Lim, Tara Miller, Luciano Potena,

health (e.g., imaging, endomyocardial biopsy) is balanced with monitoring for complications and side effects of immunosuppressive therapies. While beyond the scope of this document, it is important to note that immune function assays, gene expression profiling, and novel biomarkers as noninvasive strategies to more effectively tailor immunosuppression treatment are being investigated.<sup>437–439</sup>

**Corticosteroid minimization and withdrawal****Topic 1: Minimization of immunosuppression**

The principal goal of immunosuppression in heart transplantation (HT) is to balance prevention of allograft rejection and adverse immunotherapy effects. Unfortunately, there are no evidence-based approaches to determine the lowest effective immunosuppressive regimen for HT recipients, therefore, evaluation of drug levels along with surveillance of graft

Data from the ISHLT Registry demonstrates reduction in corticosteroid (CS) use in the intermediate- to long-term time post-transplant. However, approximately 80% of patients were reported to be taking CS at 1 year after transplant.<sup>94</sup> The two primary strategies to minimize CS exposure include: (1) CS withdrawal either early, within the first 6 months, or late – beyond 6 months post HT, and (2) CS dose minimization. CS withdrawal appears to be feasible

when combined with contemporary immunotherapy. In the TICTAC study, excellent long-term outcomes in terms of rejection, CAV, and survival were demonstrated for early CS withdrawal at 8 weeks after transplant for patients treated with tacrolimus monotherapy or tacrolimus in combination with mycophenolate mofetil (MMF).<sup>440</sup> Based on available data, steroid withdrawal is reasonable for recipients with a lower propensity to rejection (e.g., those without circulating anti-HLA antibodies, non-multiparous women, those without a history of rejection) within the first year after transplant and can be considered as early as 3 months post-transplant. Patients should be closely monitored for rejection following CS withdrawal.

- Sarcoidosis: CS remains the mainstay of treatment for most patients with sarcoidosis.<sup>441</sup> Small observational studies of patients undergoing heart transplantation for cardiac sarcoidosis who are maintained on low-dose CS have demonstrated acceptable long-term outcomes (5-year freedom from CAV was 68% vs 78% and 5-year post-transplantation survival 79% vs 83% between the sarcoid and control groups respectively) without recurrence of sarcoidosis in the allograft or progression of extracardiac disease.<sup>442, 443</sup> Therefore, long-term CS are generally recommended in patients who have been transplanted for cardiac sarcoidosis.<sup>442, 444</sup>
- Children (age  $\leq$  18years): CS use continues to decline in the pediatric HT population. In the 2018 ISHLT registry report, 66% of pediatric HT recipients were on prednisone at discharge, compared to 74% in the era from 2005 to 2009.<sup>445</sup> In a propensity matched analysis of the Pediatric Heart Transplant Study Group (PHTS), CS use at 30 days post-transplant was 64%.<sup>446</sup> At 1-year post-transplant there was no difference in rejection or malignancy, but patients that were on CS at 30 days had a higher incidence of rejection with hemodynamic compromise and a higher incidence of infection. A recent prospective, multicenter study, Clinical Trials in Organ Transplantation in Children (CTOTC-04), demonstrated that steroid avoidance (no routine use of CS beyond the first week post-transplant) in cross-match negative pediatric heart transplant recipients treated with anti-thymocyte globulin (ATG) induction results in excellent short-term survival.<sup>447</sup> All recipients were treated with tacrolimus and MMF maintenance therapy, regardless of sensitization status, and a rejection surveillance approach utilizing per protocol biopsies. CS were subsequently added at the clinician's discretion, usually in response to rejection episodes. CS use at 1-year post-transplant was 14% in non-sensitized and 18% in sensitized patients. Based on this study and prior retrospective and single center studies,<sup>446, 448</sup> steroid avoidance in cross-match negative pediatric patients treated with ATG induction is reasonable to consider.

### **Calcineurin inhibitor minimization and withdrawal**

While still the mainstay of immunosuppression in HT recipients, CNIs are associated with several potential adverse

effects including an increased risk of chronic kidney disease. Several studies have evaluated the use of proliferation signal inhibitors (PSIs) with CNI-reduction<sup>449, 450, 295</sup> or CNI withdrawal with mixed results.<sup>295, 451–453</sup> Some studies have demonstrated beneficial effects on preservation of renal function with careful patient selection when the dose of CNI is appropriately minimized, or CNI is replaced by a PSI.<sup>450, 295,454</sup> Zuckermann et al, found that patients without preexisting diabetes derived the greatest benefit of PSI on renal function from CNI withdrawal. However, patients with MMF doses  $\leq$ 1,000 mg daily had an increased risk of biopsy proven rejection, so close monitoring for rejection is warranted in CNI-free regimens.<sup>455</sup> Patients treated with PSI may develop proteinuria and therefore, screening for pre-existing proteinuria should be considered when identifying appropriate patients for a PSI-based regimen.<sup>456</sup> The MANDELA study (a multicenter, randomized, open-label, parallel group study investigating renal tolerability, efficacy, and safety of a CNI-free regimen (Everolimus and MMF) versus a CNI-regimen with Everolimus in heart transplant recipients), randomized patients at 6 months post-transplant to a CNI-free regimen with everolimus, MMF and steroids, or reduced-exposure CNI with everolimus and steroids.<sup>457</sup> Both groups had improved renal function, and rates of adverse events were not different between groups, although the CNI-free regimen group had a higher rate of biopsy proven rejection when everolimus levels were  $<$ 5 ng/mL.

The safety of initiation of PSIs early post-transplant remains an ongoing area of investigation. In the SCHEDULE (Scandinavian Heart Transplant Everolimus de novo trial with early CNI avoidance) study, subjects were assigned to low-exposure everolimus + reduced-exposure CNI or standard-exposure CNI + MMF + CS within 5 days of transplant. In the everolimus group, CNI was withdrawn at 7 to 11 weeks post-transplant and the everolimus target goals were increased.<sup>452</sup> At 12 months after transplant, subjects in the everolimus group had higher measured GFR (primary outcome), decreased intimal thickening, and a lower incidence of CAV. However, those in the everolimus group had more frequent biopsy-proven acute rejection after weeks 7 to 11. In a post-hoc analysis of this study there were no significant differences in wound complications or surgical events.<sup>458</sup> Additionally, Potena et al performed a multicenter open-label randomized trial (Everolimus in de novo Heart Transplant Recipients, EVERHEART) comparing immediate versus delayed (4-6 weeks posttransplant) PSI initiation post-transplant.<sup>308</sup> In this study, the initiation of PSI immediately post-transplant was associated with a poor safety profile, driven primarily by a higher rate of pericardial effusions. Importantly, wound healing, and efficacy as defined by hemodynamically significant rejection, graft loss, or death were similar between the two groups. Based on the variable findings from these studies and others, the ideal immunosuppressive regimen, and the optimal timing of initiation of PSIs post-transplant remains to be determined.

## Calcineurin inhibitor monotherapy

The Tacrolimus In Combination, Tacrolimus Alone Compared (TICTAC) trial compared tacrolimus monotherapy (n = 79) versus tacrolimus/MMF (n = 71) after a brief course of CS post-transplant.<sup>440</sup> At 3-year median follow up, there were no significant differences in rejection, infection, CAV, or mortality. Importantly, patients in both groups were managed with target tacrolimus blood trough levels of 8 to 10 ng/dL. With only 1 immunosuppressive agent, medical compliance is paramount. Nonetheless, the findings suggest tacrolimus monotherapy early after transplant may be considered under certain clinical settings such as intolerance to antimetabolites, severe infections, or side effects to CS therapy.<sup>459</sup> A small percentage of highly selected low rejection risk children are maintained on single drug CNI immunosuppression but reports are limited.<sup>445, 460</sup>

## PSI use in children

There has been a significant increase in the experience of PSI use in the pediatric population in the past decade.<sup>461, 462</sup> While some single center studies have described an improvement in renal function following discontinuation of CNI and use of a PSI-based regimen,<sup>463</sup> others have found no change in renal

function with CNI-discontinuation.<sup>464</sup> However, risk of graft rejection and survival was not changed in these pediatric studies, making consideration of CNI withdrawal in select pediatric patients with significant renal dysfunction a reasonable consideration.

The PHTS performed a propensity-matched study that showed from 2004 to 2013, 7% of pediatric HT recipients were on sirolimus at 1-year post-transplant.<sup>325</sup> There was no difference in survival or major transplant adverse events between the sirolimus and non-sirolimus treated groups. Interestingly, as opposed to studies in the adult HT population, there was no association between sirolimus and improved freedom from CAV, but also no association between sirolimus use and increased rejection. On the other hand, in a comparative study of CAV between a U.S. and U.K. pediatric heart transplant center, sirolimus use correlated with a reduction in CAV.<sup>435</sup>

There is an ongoing phase III, prospective, multicenter clinical trial in pediatric heart recipients aimed at investigating the efficacy (outcomes include CAV, renal function, and rejection), safety, and tolerability of everolimus and low dose tacrolimus compared to tacrolimus and MMF in the first 3 years post-transplant (TEAMMATE trial).<sup>465</sup> Ongoing pediatric specific studies are needed in order to determine the optimal immunosuppression regimen in children.

Topic 1. Minimization of Immunosuppression	
2010 Prior Guideline Recommendation	2023 Guideline Update Recommendation
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, or older patients). Class I, Level of Evidence: B	CS withdrawal can be successfully achieved within 3-12 months after HT in many low rejection risk patients. When possible, CS withdrawal should be considered to limit side effects associated with long-term CS use. <b>Class I, Level of Evidence: B</b>
Lower levels of CNIs in HT recipients should be sought when CNIs are used in conjunction with MMF (compared to AZA) because with this combination lower levels are safe and associated with lower rejection rates as well as improved renal function. Class I, Level of Evidence: B From the CKD section: In all HT recipients (adult and pediatric) with 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. <b>New Recommendation</b>	Continuing approval without change.  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. <b>Class I; Level of Evidence: B</b>  Initiation of a PSI should be done with dose reduction or withdrawal of CNI, and should be done cautiously if within 3 months of HT. <b>Class I; Level of Evidence: B</b>
A PSI may be substituted for CNI later than 6 months after HT to reduce CNI-related nephrotoxicity and CAV in low-risk recipients. Class II, Level of Evidence: C	Substituting PSI for CNI in low rejection risk adult recipients may be considered to reduce CNI-related nephrotoxicity. <b>Class IIa; Level of Evidence: B</b> <b>New Pediatric Recommendation:</b> Substitution of a PSI for CNI in pediatric HT recipients with significant renal dysfunction may be considered, although close monitoring for acute graft rejection is required for CNI-free regimens. <b>Class IIb, Level of Evidence: C</b>

(continued on next page)

*(Continued)***Topic 1. Minimization of Immunosuppression****2010 Prior Guideline Recommendation**

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.

Class IIb, Level of Evidence: B

**New Recommendation**

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.

Class IIb, Level of Evidence: C

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

Class IIb, Level of Evidence: C

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

Class IIb, Level of Evidence: C

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.

Class III, Level of Evidence: C

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.

Class III, Level of Evidence: C

**2023 Guideline Update Recommendation**

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

**Adults: Class IIa, Level of Evidence: A**

**Pediatrics: Class IIa, Level of Evidence: C**

Patients with cardiac sarcoidosis undergoing heart transplantation should be maintained on low-dose CS for preventing recurrence of sarcoidosis if clinically indicated.

**Class IIb, Level of Evidence: B**

In pediatric HT recipients, CS avoidance in selected individuals is reasonable, particularly when paired with induction immunosuppression, and minimizes complications including hypertension and CKD.

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

Continuing approval without change.

**Recommendation Removed:** combined with below. Recommendation for PSIs as they relate to CAV in children is now detailed in Topic 3: Cardiac Allograft Vasculopathy.

In pediatric and adult HT recipients, it is reasonable to substitute a PSI for MMF and decrease the CNI dose for the specific purpose of lowering CNI exposure to reduce CNI-related nephrotoxicity.

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

**Recommendation Removed:** Group consensus to delete this recommendation as the consideration for initiation of PSI within 3 months of transplant is now covered in the Class I recommendation above.

**Topic 2: Management of neurologic complications**

The spectrum of neurologic complications occurring after heart transplantation is broad, including postoperative delirium, stroke, drug side effects, central nervous system (CNS) infections, neuropathies, seizures, neurodevelopmental disabilities, encephalopathy, and post-transplantation CNS lymphomas.<sup>466, 467</sup> A preoperative history of hypertension, diabetes mellitus, smoking, stroke, and markers of vascular disease are classical risk factors for stroke following cardiac surgery.<sup>468, 469</sup> The use of MCS devices, preoperative intra-aortic balloon pump support, prolonged cardiopulmonary bypass (CPB) time, and postoperative hepatic failure contribute to higher risk in HT recipients.<sup>470</sup> While stroke risk after transplant in adult patients bridged with LVADs has been reported to be as low as 2.2%,<sup>471</sup> children <10 kg bridged with paracorporeal VADs have been reported to have an 8% incidence of stroke before heart transplant hospital discharge, a rate that far exceeds age matched controls who did not require VAD

support.<sup>472</sup> In adults, older age and the presence of extracranial carotid artery stenosis increases the risk of post-transplant stroke.<sup>473</sup>

Headache, tremor, seizure, thrombotic microangiopathies (TMA), and posterior reversible encephalopathy syndrome (PRES) occur following heart transplantation and have been associated with CNI therapy and hypertension.<sup>474, 475</sup> Some of these symptoms may improve with lowering of CNI dose. PRES can present with headache, visual changes, and seizures in the setting of hypoattenuated cortical and subcortical lesions seen on T2-weighted magnetic resonance brain imaging.<sup>475</sup> In general, PRES will subside with control of blood pressure and reduction of CNI dose, as patients with CNI-associated PRES generally have supratherapeutic levels.<sup>476</sup> In some cases, conversion to an alternative CNI or CNI withdrawal is required.<sup>477, 478</sup> Care must be taken to prevent sub-optimal anti-rejection therapy dosing when CNI is withdrawn or reduced in dose.

The causes of seizures after HT include adverse effects of antirejection therapy, electrolyte abnormalities, osmolar



change, CNS infection, ischemic or hemorrhagic stroke, tumor (including central nervous system post-transplant lymphoproliferative disorder), and a history of epilepsy before transplantation.<sup>479, 480</sup> Patients with epilepsy, or those requiring antiepileptic drugs, require careful consideration due to substantial drug-drug interactions with standard post-transplant immunosuppression.<sup>481</sup> In general, phenytoin, phenobarbital, carbamazepine, and valproic acid should be avoided and fosphenytoin should be used with caution.<sup>481</sup>

HT recipients universally share multiple risk factors for ICU delirium.<sup>482</sup> This includes hemodynamic instability, preexisting stroke, use of benzodiazepines, and administration of CS and CNIs.<sup>483</sup> Additional research is needed to understand how HT recipients are affected in the longer term by ICU delirium.

Peripheral neuropathy due to systemic diseases before HT may preclude long-term survival post-transplant or interfere with cardiac rehabilitation. Patients with diabetes mellitus and heart disease can have peripheral neuropathy and need to be evaluated thoroughly before HT. Postoperative peripheral nervous system complications most commonly include brachial plexopathy, peroneal nerve mononeuropathy, critical illness neuropathy or myopathy, and injury to the recurrent laryngeal nerve with resulting vocal cord paralysis.<sup>484–486</sup> Although patient survival after transplantation may not be affected by these complications, they do contribute to the morbidity of the procedure and prolong rehabilitation time. Careful patient management and attention to patient positioning and monitoring could avoid these peripheral nervous complications.<sup>473</sup>

### Neurodevelopmental delays and disabilities

It is increasingly recognized that children who have undergone cardiac surgery are at increased risk for neurodevelopmental disabilities including attention deficit hyperactivity

disorder (ADHD), anxiety, depression, autism spectrum disorders, delays in fine and gross motor skills, impairment in social cognition, and other issues with adaptive functioning.<sup>467, 487</sup> Children at highest risk include those who have required ECMO and MCS.<sup>488–490</sup> The Berlin Heart EXCOR pediatric VAD, the most commonly used VAD to bridge children < 30 kg to heart transplantation, was associated with neurological dysfunction in 30% of children during the initial experience, though stroke rates are now below 10% with the use of bivalirudin anticoagulation.<sup>491, 492</sup> Risk of neurodevelopmental disability is higher in infant heart transplant recipients and those who have undergone prior surgical palliations for congenital heart disease.<sup>493, 494</sup> Given the high incidence of neurodevelopmental delay and disability, careful screening for developmental delays should occur during routine post-transplant care. HT recipients with a history of congenital heart disease or MCS should be referred for early intervention or formal neurodevelopmental evaluation.<sup>467</sup>

### Psychiatric comorbidities

Both adults and children are at risk for psychiatric comorbidity after transplant.<sup>467</sup> The first year after a transplant is characterized as a time of readjustment and rehabilitation; however, transplant recipients often report that physical and emotional recovery takes longer than they would have personally expected.<sup>495</sup> HT recipients must adjust to a complex post-transplant regimen which includes multiple medications and lifestyle restrictions. The literature exploring longer term issues for HT recipients has demonstrated that fears about death, body image concerns, financial concerns, and family difficulties are common. The constant focus on risk of rejection and adherence to anti-rejection medications can lead to anxiety and depression.<sup>496, 497</sup> Both HT recipients and their parents or caregivers are at risk for posttraumatic stress disorder and many recipients benefit from psychological screening and treatment.<sup>498–500</sup>

## Topic 2. Management of Neurologic Complications

### 2010 Prior Guideline Recommendation

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.

Class I, Level of Evidence: C

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

Class I, Level of Evidence: C

PRES in HT recipients should be managed with a reduction of CNI doses or substitution with an alternative CNI.

Class I, Level of Evidence: C

### New recommendation

### 2023 Guideline Update Recommendation

Management of HT recipients with new onset seizures not due to stroke or structural brain disease should include reduction of CNI doses (taking into consideration the risk of inadequate immunosuppression) and correction of hypomagnesemia, if present.

**Class I, Level of Evidence: C**

Continuing approval without change.

PRES in HT recipients should be managed with gradual blood pressure reduction and withdrawal or reduction of CNI along with substitution for an alternate immunosuppressive agent or an alternate CNI.

**Class I, Level of Evidence: C**

Children are at high risk for neurodevelopmental delay and disability after heart transplantation. Careful screening for

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## Topic 2. Management of Neurologic Complications

## 2010 Prior Guideline Recommendation

HT recipients who continue to experience seizures after a reduction in CNI dose may benefit from CNI withdrawal and substitution with a PSI (SRL, everolimus [EVL]).

Class IIb, Level of Evidence: C

**New recommendation**

## 2023 Guideline Update Recommendation

developmental delays should occur during routine post-transplant and primary care. HT recipients with a history of congenital heart disease or MCS should be referred for early intervention or formal neurodevelopmental evaluation. **Class I, Level of evidence C**

HT recipients who continue to experience seizures after reduction in CNI dose may benefit from CNI withdrawal and substitution with a PSI.

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

For HT candidates with a history of epilepsy who require antiepileptic therapy, antiseizure medication choice should balance the efficacy for seizure reduction and potential for drug-drug interactions with immunosuppression medications commonly used after HT.

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

**Topic 3: Cardiac allograft vasculopathy****Screening and diagnosis**

Cardiac allograft vasculopathy (CAV) remains highly prevalent and a leading cause of death after heart transplantation.<sup>501</sup> Imaging surveillance is challenging due to diffuse involvement of the coronary epicardial arteries, branch vessels, and microvasculature. In 2010, the ISHLT proposed invasive coronary angiography as the gold standard for diagnosing CAV, and standardized grading of angiographic severity (Table 11, adapted from<sup>502</sup>). Angiography is widely accessible and the ISHLT CAV<sub>0-3</sub> classification has

been shown to be associated with long-term survival.<sup>279, 503, 504</sup> A large registry study in the pediatric heart transplant population demonstrated an association between graft dysfunction and increased risk of graft loss in children with CAV.<sup>279</sup> Importantly, in this study the presence of 1 functional abnormality was associated with an increased risk of graft loss even in those with mild CAV (CAV<sub>1</sub>).

Concurrent intravascular imaging using intravascular ultrasound (IVUS) or optical coherence tomography (OCT) permits vessel wall evaluation for neointimal hyperplasia in early CAV, plaque morphology as well as donor-transmitted coronary artery disease (CAD). Many studies have shown worse clinical outcomes in patients without

**Table 11** Recommended Nomenclature for Cardiac Allograft Vasculopathy

ISHLT CAV0 (Not significant): No detectable angiographic lesion

ISHLT CAV1 (Mild): Angiographic left main (LM) <50%, or primary vessel with maximum lesion of <70%, or any branch stenosis <70% (including diffuse narrowing) without allograft dysfunction

ISHLT CAV2 (Moderate): Angiographic LM <50%; a single primary vessel ≥70%, or isolated branch stenosis ≥70% in branches of 2 systems, without allograft dysfunction

ISHLT CAV3 (Severe): Angiographic LM ≥50%, or two or more primary vessels ≥70% stenosis, or isolated branch stenosis ≥70% in all 3 systems; or ISHLT CAV1 or CAV2 with allograft dysfunction (defined as LVEF ≤45% usually in the presence of regional wall motion abnormalities) or evidence of significant restrictive physiology (which is common but not specific; see text for definitions)

**Definitions**

- A "Primary Vessel" denotes the proximal and middle 33% of the left anterior descending artery, the left circumflex, the ramus and the dominant or co-dominant right coronary artery with the posterior descending and posterolateral branches.
- A "Secondary Branch Vessel" includes the distal 33% of the primary vessels or any segment within a large septal perforator, diagonals and obtuse marginal branches or any portion of a non-dominant right coronary artery.
- Restrictive cardiac allograft physiology is defined as symptomatic heart failure with echocardiographic E to A velocity ratio >2 (>1.5 in children), shortened isovolumetric relaxation time (<60 msec), shortened deceleration time (<150 msec), or restrictive hemodynamic values (Right Atrial Pressure >12 mm Hg, Pulmonary Capillary Wedge Pressure (PCWP) >25 mm Hg (>15 mm Hg in children\*), Cardiac Index <2 l/min/m<sup>2</sup>)

\*Modified PCWP threshold in children based on.<sup>279</sup>

angiographic disease but who have intimal thickening on IVUS as early as 6 weeks post-transplant (donor disease) or IVUS only disease progression up to 5 years after transplant.<sup>70, 505, 506</sup> OCT has 10-fold higher resolution than IVUS, but lower tissue penetration that limits assessment of deep plaque features. Similar to IVUS, early post-transplant OCT studies show significant increase in intimal volume occurring without appreciable reduction in coronary lumen on angiography.<sup>507–509</sup> Layered fibrotic plaque on OCT has been observed as the predominant plaque morphology in early CAV and an independent predictor of nonfatal CAV progression.<sup>510</sup> Relevant limitations for both IVUS and OCT include high catheter costs, availability, anticoagulation requirement, risks associated with instrumenting the coronary artery, evaluation limited to the major epicardial vessels, and patient size (particularly in children).

Invasive coronary angiography and IVUS are typically performed every 1 to 2 years, particularly in the absence of renal impairment. However, the optimal frequency for surveillance coronary angiography in both adults and children is not well defined. More frequent evaluation may be considered following percutaneous coronary intervention for evaluation of in stent restenosis and progression of CAV, as well as in children after rejection with hemodynamic compromise or new onset CAV given the significant early hazard for CAV development and/or progression.<sup>511</sup> Less frequent evaluation may be reasonable for patients with an increased risk of complications, such as contrast nephropathy or children determined to be low risk for CAV (e.g., younger age at transplant, non-HLA sensitized, no prior rejection).<sup>512</sup>

Invasive assessment of coronary physiology for endothelial and microvascular dysfunction have been investigated as surrogate measures of microvascular disease. In patients with CAV involving the microvasculature, reduced coronary flow reserve (CFR), increased index of microcirculatory resistance (IMR), and abnormal vasoconstrictor response to acetylcholine have been observed.<sup>513</sup> These abnormalities are independent predictors of subsequent angiographic CAV, ischemic events, allograft failure, and death.<sup>513–515</sup> While use of these modalities is reasonable, prospective studies are needed to define the role of intracoronary flow in post-transplant surveillance, including as a prognostic indicator and as a guide for revascularization in CAV.

Various non-invasive imaging techniques are used for CAV surveillance, particularly in patients unable to undergo invasive evaluation. Most studies demonstrate reasonable diagnostic performance for detecting angiographic stenosis  $\geq 50\%$  but limited sensitivity for detecting less severe ISHLT grade CAV<sub>1</sub>, early coronary intimal thickening, and microvascular disease. Due to the absence of robust diagnostic and prognostic evidence supporting any single modality, the choice of noninvasive surveillance is largely dependent on local center expertise.

Large contemporary analyses of dobutamine stress echocardiography (DSE) have reported very low sensitivity for detecting angiographic CAV. The largest retrospective cohort study of 497 patients with 1,243 DSE performed at 8.7 median years post-transplant reported a low prevalence

of an abnormal result in 1.8% of patients and only 7% sensitivity for angiographic disease.<sup>516</sup> Furthermore, the presence of ischemia on DSE did not predict clinical outcomes. In another study of 109 patients at 2.7 median years from transplant, DSE had 0% sensitivity for ISHLT grade CAV<sub>1-2</sub>.<sup>517</sup> A single center study of exercise stress echocardiography in children showed high sensitivity (89%) and specificity (92%) for identifying CAV<sub>1-3</sub> but larger multi-center cohort studies have not been performed.<sup>518</sup> Small studies have shown improved diagnostic accuracy of DSE when combined with speckle tracking for strain imaging or Doppler contrast echocardiography for determination of coronary flow reserve.<sup>519–521</sup> However, current clinical application is limited by requirements for specialized expertise to perform and interpret these additional tests.

Nuclear myocardial perfusion imaging is also used for non-invasive CAV evaluation. Single-photon emission computed tomography (SPECT) myocardial perfusion imaging studies show prognostic utility but low to moderate diagnostic accuracy for CAV.<sup>522, 523</sup> In one published series of 110 patients, SPECT had up to 84% sensitivity and 78% specificity for detecting  $\geq 50\%$  stenosis on angiography.<sup>522</sup> However, in a more recent large single center study, the area under the curve for the diagnosis of significant CAV (CAV<sub>2-3</sub>) by SPECT with myocardial perfusion imaging was only 0.65.<sup>524</sup> The limited diagnostic performance of SPECT is partly owing to diffuse CAV disease causing global perfusion abnormalities that are more likely to be missed in the absence of a normal reference segment.

There is growing interest in absolute myocardial blood flow quantification using positron emission tomography (PET) to detect homogenous reductions in myocardial blood flow and assess both the coronary macro- and microvasculature.<sup>525–527</sup> In a retrospective study of 66 patients evaluated with ammonia-13 PET at a mean of 11.8 years post-transplant, Bravo and colleagues showed good discriminative ability of combined stress flow  $< 1.7$ , regional perfusion abnormality, and left ventricular ejection fraction  $\leq 45\%$  for ISHLT moderate to severe CAV<sub>2-3</sub> (area under the curve 0.88).<sup>525</sup> Similarly, a rubidium-82 PET study of 80 patients from separate derivation and validation cohorts combining corrected myocardial flow reserve  $< 2.9$ , stress myocardial blood flow  $< 2.3$ , and coronary vascular resistance  $> 55$  demonstrated 83 to 88% sensitivity for  $\geq 1$  abnormal parameter and 88–90% specificity for 3 abnormal parameters to detect CAV as defined by maximal intimal thickness  $\geq 0.5$  mm on IVUS.<sup>528</sup> Additionally, several studies have shown prognostic utility of PET measured myocardial flow reserve and/or stress flow after heart transplantation.<sup>525, 526, 529, 530</sup> The emerging evidence for PET in CAV has, however, not led to broad clinical implementation due to accessibility and lack of consensus on optimal parameters and thresholds for diagnosis and prognostication.

Cardiac magnetic resonance (CMR) measured semi-quantitative myocardial perfusion reserve (MPR) and diastolic strain have also been evaluated for detecting CAV.<sup>531, 532</sup> Miller et al<sup>531</sup> demonstrated diagnostic superiority of CMR derived MPR over coronary angiography

with an area under the curve of 0.89 for moderate CAV, which was defined as IVUS plaque volume index above the 50th percentile. Erbel et al<sup>533</sup> showed MPR and diastolic strain rate are significantly reduced in patients with microvascular CAV and are independent predictors of microvasculopathy on endomyocardial biopsy. Delayed gadolinium enhancement, representing myocardial fibrosis, in infarct typical and atypical patterns have been described in CAV including in patients with absent or mild angiographic disease.<sup>534, 535</sup> A cohort study of 152 patients at a mean of 5.0 years post-transplant reported an 18% prevalence of myocardial fibrosis that was increased with higher ISHLT CAV grades. They also demonstrated independent incremental prognostic value for the extent of fibrosis for all-cause death or major adverse cardiac events: hazard ratio 1.06 per 1% increase in fibrosis, 95% CI 1.03 to 1.09,  $p < 0.001$ .<sup>536</sup> Important limitations for CMR in the transplant population include allograft denervation with high resting heart rates reducing image quality, pacemakers/retained metal contraindicating CMR, and the risk of nephrogenic systemic fibrosis in patients with severe renal impairment. In addition, evidence of accumulation of gadolinium in the brain of patients after cumulative exposure raises some concern for using this method as a routine surveillance technique until further information is available.<sup>537</sup>

Technological advancements in coronary computed tomographic angiography (CCTA) have led to adoption as a non-invasive alternative to invasive coronary angiography. A meta-analysis of 13 prospective CCTA studies in 615 HT patients showed mean weighted 94% sensitivity, 92% specificity, 99% negative predictive value, and 67% positive predictive value for detecting stenosis  $\geq 50\%$  on invasive angiography.<sup>538</sup> The addition of quantitative plaque analysis may also improve sensitivity for CAV detection.<sup>539, 540</sup> Potential barriers for CCTA for CAV surveillance include poor visualization of smaller  $< 2$  mm diameter vessels, motion artifacts with high post-transplant heart rates in infants and young children, need for intravenous contrast administration and radiation exposure.

Several blood-based biomarkers have been identified which are associated with CAV in both pediatric and adult heart transplant recipients.<sup>541, 542</sup> In particular, vascular endothelial growth factor A (VEGF-A) has been demonstrated to identify patients at risk for the subsequent development of angiographic CAV in children.<sup>541, 543</sup> Follow-up prospective cohort studies using VEGF-A based screening are necessary in pediatric heart transplant recipients to identify optimal clinical usage of this biomarker.

### **Immunosuppressive strategies for prophylaxis or treatment of CAV**

Many randomized controlled studies have shown treatment with the PSIs, sirolimus or everolimus, as part of CNI reduced- or CNI free- (replaced by AZA or MMF) regimens reduces CAV incidence and progression.<sup>544–547</sup> A meta-analysis of 14 PSI studies with patient sample sizes of 23 to 644 demonstrated 61% relative risk reduction in CAV for PSI.<sup>548</sup> Cellular rejection rates are increased without short-

term mortality when PSIs have been used without CNI early post-transplant, so careful rejection surveillance is necessary for CNI-free regimens.<sup>457, 548, 549</sup> The timing of PSI initiation after transplant has also been examined (and discussed previously) with most studies demonstrating attenuated CAV progression in patients treated de-novo or early ( $\leq 2$  years) post-transplant. This differential beneficial effect on CAV is postulated to be related to differing plaque composition with greater fibrous component in early disease compared to predominant necrotic and calcific components in late disease.<sup>550, 551, 299</sup> A recent large single-center non-randomized retrospective analysis of 402 patients comparing CNI ( $n = 134$ ) vs sirolimus with complete CNI withdrawal ( $n = 268$ ) observed significant attenuation of IVUS assessed plaque burden for the sirolimus group. Moreover, the increase in plaque volume and plaque index were significantly lower for patients converted to sirolimus early (median 0.7 years) compared to late (median 4.4 years) post-transplant.<sup>299</sup> Furthermore, all-cause mortality (hazard ratio 0.47, 95% CI 0.31–0.70,  $p < 0.001$ ) and CAV-related events (hazard ratio 0.35, 95% CI 0.21–0.59,  $p < 0.001$ ) were lower in the sirolimus group, with similar rates of treated rejection and adverse events in both groups.<sup>299</sup> Data in children for early conversion to PSI is currently lacking but is the subject of the ongoing TEAMMATE study comparing outcomes at 3 years in patients randomized to either everolimus and low-dose tacrolimus or tacrolimus and MMF at 6 months post-transplant.<sup>465</sup> Together, these data support consideration of early conversion to PSI for CAV prevention or treatment in heart transplant recipients. Importantly, the current lack of approval for PSI use in heart transplantation in some countries as well as the tolerability profile of PSIs may restrict use to selected patient subgroups.<sup>552</sup>

### **Percutaneous revascularization**

Percutaneous coronary intervention (PCI) can be undertaken for obstructive focal CAV disease. In a single center analysis of 393 adult patients with CAV, long-term survival was higher in patients with disease amenable to PCI compared to those not treatable with PCI.<sup>553</sup> In a large multicenter cohort of pediatric heart transplant recipients, only 2% of patients underwent PCI with donor age  $> 30$  years being associated with need for PCI.<sup>554</sup> Freedom from graft loss was only 61% within 12 months of PCI, though the majority of the graft loss group underwent retransplantation.

There are no randomized trials of drug-eluting stents (DES) compared to bare metal stents (BMS) in the treatment of CAV. Observational studies have reported lower early in stent restenosis rates with newer second generation DES compared to BMS and first-generation DES.<sup>555–557</sup> In these studies, 5 to 15% in stent restenosis was reported at 6 months and 23% by 12 months.<sup>555, 557</sup> In a study of everolimus-eluting stents,<sup>558</sup> the one and 3-year target lesion revascularization rates were  $5.1 \pm 2.5\%$  and  $21.2 \pm 6.3\%$ , target vessel revascularization rates were  $17.1 \pm 4.5\%$  and  $46.2 \pm 7.8\%$ , and non-target vessel revascularization rates were  $26.3 \pm 5.4\%$  and  $58.0 \pm 7.0\%$ . Hence, it is

reasonable to consider repeat angiography at 6 months following PCI to assess for in stent restenosis, progression of disease, and development of de novo lesions. The rates of death or myocardial infarction appear to be comparable

between BMS and DES.<sup>559</sup> Drug-coated balloon angioplasty<sup>560</sup> and bioresorbable stents<sup>561</sup> have also been used in the treatment of focal disease but data are limited and no conclusion can be made of their effectiveness.

Topic 3. Cardiac Allograft Vasculopathy	2023 Guideline Update Recommendation
2010 Prior Guideline Recommendation	2023 Guideline Update Recommendation
<p>Primary prevention of CAV in HT recipients should include strict control of cardiovascular risk factors (hypertension, diabetes, hyperlipidemia, smoking, obesity) as well as strategies for the prevention of CMV infection. Class I, Level of Evidence: C</p>	<p>Primary prevention of CAV in HT recipients should include strict control of cardiovascular risk factors (hypertension, diabetes, hyperlipidemia, smoking, obesity), education on physical activity and healthy diet, as well as strategies for the prevention of CMV infection. <b>Class I, Level of Evidence: C</b></p>
<p>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). Class I, Level of Evidence: A</p>	<p>Continuing approval without change.</p>
<p>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. Class I, Level of Evidence: C</p>	<p>Coronary angiography should be performed to assess the development of CAV and angiograms should be graded according to the 2010 ISHLT nomenclature. <b>Class 1, Level of Evidence: B</b> Annual or biannual coronary angiography evaluation should be considered. Less frequent evaluation may be undertaken in patients at increased risk of complications, especially those with renal insufficiency. <b>Class I, Level of Evidence: C</b></p>
<p>Follow-up coronary angiography is recommended at 6 months after a PCI because of high restenosis rates in HT recipients. Class I, Level of evidence: C</p>	<p>Follow-up coronary angiography is recommended at 6 months after a PCI for evaluation of in stent restenosis and progression of CAV. <b>Class I, Level of Evidence: C</b></p>
<p>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. Class I, Level of Evidence: C</p>	<p>Selective coronary angiography is the investigation of choice for the diagnosis of CAV in pediatric HT recipients and should be graded according to the 2010 ISHLT nomenclature. A modified pulmonary capillary wedge pressure cutoff &gt;15 mm Hg is used to define restrictive physiology. <b>Class I, Level of Evidence: B</b> Surveillance coronary angiography should be considered in pediatric HT recipients at regular intervals. A screening frequency of every 1 to 2 years is reasonable. <b>Class I, Level of Evidence: C</b></p>
<p>A baseline coronary angiogram at 4 to 6 weeks after HT may be considered to exclude donor CAD. Class IIa, Level of Evidence: C 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 CAD, to detect rapidly progressive CAV, and provide prognostic information. Class IIa, Level of Evidence: B</p>	<p>Baseline IVUS in conjunction with coronary angiography at 4 to 6 weeks after HT and at 1 year after HT should be considered to exclude donor transmitted or derived CAD, to detect rapidly progressive CAV, and provide prognostic information. <b>Adults: Class IIa, Level of Evidence: B</b> Baseline IVUS in conjunction with coronary angiography at 1 year after HT can be considered in pediatric recipients to exclude donor CAD, to detect rapidly progressive CAV, and provide prognostic information. Patient size and institutional expertise in performing IVUS in children is an important consideration in this surveillance approach. <b>Class IIb, Level of Evidence: C</b></p>
<p>In HT recipients with established CAV, the substitution of MMF or AZA with a PSI can be considered. Class IIa, Level of Evidence: B</p>	<p>Substitution of MMF or CNI with a PSI should be considered to prevent and delay progression of CAV, especially within 2 years of HT. <b>Class I, Level of Evidence: A</b></p>
<p>A PSI can be used in pediatric HT recipients who develop CAV, but the effect of PSIs on the progression of CAV in children is unknown. Class IIa, Level of Evidence: C IVUS can be safely used in older pediatric HT recipients to assess CAV Class IIa, Level of Evidence: C</p>	<p>A PSI can be used in pediatric HT recipients who develop CAV. <b>Class IIa, Level of Evidence: C</b> Continuing approval without change.</p>

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## Topic 3. Cardiac Allograft Vasculopathy

## 2010 Prior Guideline Recommendation

**New recommendation**

Evaluation of CFR in conjunction with coronary angiography may be useful for the detection of small vessel CAD, which is a manifestation of CAV.

Class IIa, Level of Evidence: C

**New recommendation**

Treadmill or DSE 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.

Class IIa, Level of Evidence: B

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

Class IIa, Level of Evidence: C

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

Class IIa, Level of Evidence: C

Ultrafast 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.

Class IIb, Level of Evidence: C

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.

Class IIb, Level of Evidence: C

**New recommendation**

## 2023 Guideline Update Recommendation

OCT in conjunction with coronary angiography may be considered at 4 to 6 weeks and 1 year after HT to detect donor transmitted or derived CAD and provide prognostic information.

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

Evaluation of intracoronary flow (CFR, IMR) in conjunction with coronary angiography may be useful for the detection of small vessel CAD, which is a manifestation of CAV.

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

PET myocardial blood flow quantification and perfusion imaging may be used for noninvasive detection of CAV and to provide prognostic information.

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

DSE and SPECT myocardial perfusion imaging have low sensitivity for detection of CAV but may be useful for prognostication in HT recipients unable to undergo invasive evaluation, CCTA or PET.

**Adult: Class IIb, Level of Evidence: B**

**Pediatrics: Class IIa, Level of Evidence: B**

PCI with drug-eluting stents, as opposed to BMS, is recommended in both adults and children with CAV for appropriate discrete lesions.

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

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

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

CCTA may be used as a noninvasive alternative to coronary angiography for the detection of CAV in  $\geq 2$  mm epicardial vessels. Higher resting heart rates in HT patients may limit the technical quality of the study.

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

CMR myocardial perfusion reserve and delayed gadolinium enhancement assessment may be considered in the evaluation of CAV in HT recipients.

**Class IIb, Level of Evidence C**

**Topic 4: Malignancy after heart transplantation**

Malignancy after heart transplantation remains a significant cause of morbidity and mortality in adult and pediatric recipients. ISHLT registry data demonstrates a cumulative prevalence of all types of malignancy post-heart transplantation in adults of 16% in 5-year survivors and 28% in 10-year survivors.<sup>390</sup> In adults, skin cancer remains the most common post-transplant malignancy, followed by prostate and lung cancer, with lymphoma being uncommon.

In a recent analysis of the UNOS registry, donor history of malignancy was not independently associated with a change in 10-year survival.<sup>562</sup> However, a history of pre-transplant malignancy in the recipient was associated with

an increased risk of post-transplant malignancy, especially skin malignancies. Older recipient age, male sex, and white race were also risk factors for post-transplant malignancy in this cohort of patients.<sup>563</sup>

In the pediatric age group, post-transplant malignancy is less common with a prevalence of 10% in 10-year survivors and almost exclusively due to lymphoma.<sup>445</sup> Post-transplant lymphoproliferative disorder (PTLD), often driven by Epstein-Barr virus (EBV) and usually of B-cell origin, is the most common malignancy in pediatric recipients. In pediatric heart recipients, the probability of freedom from PTLT is 98%, 95%, and 90% at 1-, 5-, and 10 years post-transplant, respectively.<sup>564</sup> Children between the age of 1 and 10 years old had the highest

risk of developing PTLD.<sup>564</sup> In a recent single center study of PTLD in pediatric solid organ transplant recipients, the most frequent PTLD site was tonsillar/adenoidal (34%), closely followed by gastrointestinal (32%).<sup>565</sup> In those surviving beyond 10 years, malignancy in general was the primary cause of death in 4% of pediatric heart recipients.<sup>445</sup>

### **Role of immunosuppression**

Chronic immunosuppression has been implicated as a risk factor for malignancy. Malignancy prevention in the pediatric and adult population includes minimization of immunosuppression as clinically tolerated.<sup>566</sup> There remains mixed results when considering the impact of induction therapy on risk of development of PTLD.<sup>567</sup> Analysis of the PHTS registry did not demonstrate any association with induction therapy and the risk of PTLD in children.<sup>340</sup> In the current era, due to lower induction dosing and minimization of maintenance immunosuppression the risk of PTLD may be a lesser consideration when determining whether to use induction therapy.

### **EBV screening and monitoring**

Determination of recipient and donor EBV serostatus is important for risk stratification to inform prevention strategies. Anti-viral capsid antigen (VCA) IgG and anti-EBV nuclear antigen-1 (EBNA) IgG are serologic tests most often used for EBV serostatus assignment. EBV exposure history is difficult to determine in infants <12 months because of the presence of maternal antibody. Pre- and post-transplant EBV serology results are also difficult to interpret in the presence of passive antibody from transfused blood and after receipt of immunoglobulin products. Direct measurement of EBV DNA in peripheral blood has replaced seroconversion for the diagnosis of primary EBV infection, as the latter responses are often delayed. EBV viral load surveillance and preemptive interventions in patients who are EBV-seronegative pretransplant who receive a seropositive donor are recommended by the recent guidelines of the American Society of Transplantation (AST).<sup>568</sup>

Children between 1 and 10 years of age receiving EBV mismatch organs (donor positive; recipient negative) are at particular risk of PTLD.<sup>564</sup> Regular monitoring should occur in the first post-transplant year until EBV DNAemia is detected. Viral load surveillance and preemptive strategies are not routinely recommended for solid organ transplant patients who are EBV seropositive pretransplant.

There remains no evidence that prophylactic antiviral therapy or IVIG is protective against the development of EBV.<sup>569</sup> Adoptive immunotherapy using either in vitro expanded autologous or HLA-matched banked third-party donor polyclonal EBV-specific cytotoxic T-lymphocytes has also been used for PTLD prevention, given either to all high-risk patients or preemptively in response to EBV DNAemia. This prevention approach has been most extensively evaluated in HSCT recipients; data

in solid organ transplant recipients is limited. Access, cost, and lack of definitive evidence of effectiveness in the solid organ transplant population prohibits widespread implementation of this approach.<sup>570</sup>

### **Treatment**

PTLD care should be provided at transplant centers by physicians with expertise in the management of this complex patient population. The treatment of PTLD is particularly challenging and there is an evolving body of evidence to suggest that rituximab monotherapy could be considered in select patient populations.<sup>571</sup> A recent phase II clinical trial was performed in adult SOT recipients with CD20<sup>+</sup> PTLD that did not respond to a decrease in immunosuppression.<sup>571</sup> Patients were treated with induction of rituximab (4 weekly doses), followed by restaging, with responders continuing on rituximab every 21 days × 4 doses. Patients that had progression of PTLD after rituximab induction were treated with rituximab and cytotoxic chemotherapy (CHOP- cyclophosphamide, doxorubicin, vincristine, and prednisone) every 21 days for 4 courses. Using this protocol, 111 of 126 patients had a complete or partial response, suggesting rituximab monotherapy could be successful in a subset of patients. The experience in children is less robust, but similar, with studies demonstrating success in children with resistant PTLD treated with rituximab monotherapy.<sup>572</sup>

Similar to what has been previously described, recent studies continue to identify a lower risk of malignancy development with the use of MMF or PSI (e.g., everolimus, sirolimus) for maintenance immunosuppression compared to CNI and AZA.<sup>573, 574</sup> However, there are not sufficient data to either prescribe specific protocols for immunosuppression reduction or provide recommendations for or against switching to a PSI. Additionally, antiviral therapy as a sole preemptive intervention is not recommended.<sup>568</sup>

Adoptively transferred multispecific or EBV-specific T cells generated from eligible, third-party donors have been studied mainly in recipients of HSCT and in a limited number of solid organ transplant recipients with promising results. Off-the-shelf EBV-specific T cell immunotherapy demonstrates promise as an immediately available potential therapy for patients with EBV-associated lymphoma after transplantation.<sup>575, 576</sup>

### **Screening and follow-up**

There is little data to support malignancy screening recommendations specific to the heart transplant recipient and approaches remain variable. In general, malignancy screening in the heart transplant recipient is the same as for normal individuals as was outlined in the previous guideline document. Skin cancer is the most common malignancy in the adult heart transplant population and a recent expert consensus statement for timing of initial skin cancer screening in adult solid organ transplant recipients was developed using Delphi methodologies.<sup>577</sup>

#### Topic 4. Malignancy After Heart Transplantation

##### 2010 Prior Guideline Recommendation

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

Class I, Level of Evidence: C

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

Class I, Level of Evidence: C

Initial evaluation and therapeutic plan for PTLD in HT recipients should be done at the transplant center by physicians familiar with transplant-associated malignancies.

Class I, Level of Evidence: C

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.

Class I, Level of Evidence: C

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

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

**New recommendation**

##### 2023 Guideline Update Recommendation

Recommendations regarding screening for solid organ tumors (e.g., breast, colon, prostate, and lung cancer) in the general population should also be followed in HT recipients.

**Class I, Level of Evidence: C**

Continuing approval without change

**New comment:** Rate of skin cancer is incredibly small in children (0.03% in 5-year survivors and 0.12% in 10-year survivors). Routine skin care should be provided for pediatric heart recipients, but any skin lesions identified after transplantation should be carefully evaluated.

Continuing approval without change

Continuing approval without change

**Recommendation removed: minimization of immunosuppression covered in Topic 1.**

Use of rituximab monotherapy for treatment of adult and pediatric CD20+ PTLD that is not responsive to a reduction in immunosuppression is reasonable.

**Adults: Class IIa, Level of Evidence: B**

**Pediatrics: Class IIa, Level of Evidence: C**

#### Topic 5: Chronic kidney disease after heart transplantation

The pathophysiology of renal dysfunction in the early post-transplant period differs from late renal dysfunction. Acute renal failure early post-transplant is related to several factors including pretransplant renal function<sup>578</sup> and the complexity of the transplant. Using data from the UNOS registry, Kilic et al<sup>579</sup> developed a risk index for postoperative renal failure (defined as new-onset acute renal failure requiring postoperative dialysis). In this cohort of 14,635 heart transplant patients, 1,128 (7.7%) patients developed acute renal failure. Thirteen factors were included in this risk index including donor age, ischemic time, and recipient factors (e.g., pretransplant creatinine clearance, bilirubin, and diabetes). The proportion of patients with renal failure requiring dialysis that persisted beyond the early postoperative phase was not reported.

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function (albuminuria, electrolyte, or other abnormalities due to tubular disorders and/or abnormalities on imaging or histology) which is present for > 3 months. Using a glomerular filtration rate (GFR) threshold of 30 mL/min/1.73 m<sup>2</sup>, the incidence of CKD has been reported to be 1.9%, 10.9%, and 21%, at 1, 5, and 10 years,

respectively in adult non-renal transplant recipients.<sup>580</sup> Pre-transplant renal impairment related to heart failure, acute kidney injury from hypotension, vasoconstrictor use and cardiopulmonary bypass, hypertension, diabetes, and nephrotoxic medications contribute to the development of CKD.<sup>581</sup>

The acute toxicities of CNI (e.g., vasoconstriction, toxic tubulopathy, and in some cases thrombotic microangiopathy) in a milieu that often includes ischemic, diabetic, and hypertensive nephropathy can lead to worsening renal function. In the longer term, CNI can induce irreversible changes (e.g., hyaline arteriopathy, interstitial fibrosis and focal segmental glomerulosclerosis) and progressive renal disease, even in the absence of vulnerable kidneys before heart transplant. Hence, CNI is a major, but not the sole, cause of post-transplant CKD. The implications are:

- (i) Patients will experience different trajectories in their renal function early post-transplant based on the pathophysiology. For example, improvement in renal function related to reversal of heart failure-related cardiorenal syndrome may initially outweigh CNI toxicity effects, which may result in early improvement in GFR. The initial improvement in renal function is typically followed



by a gradual decline in GFR (2.2-2.9 mL/min/1.73 m<sup>2</sup>/year)<sup>582</sup>;

- (ii) Management of post-transplant CKD must address the multiple risk factors including hypertension and diabetes in accordance with current recommendations<sup>583, 584</sup> (see also Task Force 3, Topic 6. Management of Cardiovascular Risk after Heart Transplantation).
- (iii) Minimizing CNI exposure with conversion to PSI may improve renal function – shorter time from transplant to conversion is associated with greater improvement,<sup>585, 586</sup> but improvement in GFR may be tempered by the presence of concomitant risk factors<sup>455, 587</sup> (see Topic 1, Minimization of Immunosuppression).

Anemia is common post-heart transplant, especially in association with CKD. Iron supplementation (if iron-deficient) and erythropoiesis-stimulating agents can minimize transfusions and improve quality of life. However, a series of randomized trials showed that normalizing hemoglobin level (>13 g/dL) in pre-dialysis patients with CKD increased mortality, cardiovascular events, and end stage renal disease (ESRD) compared to a more conservative hemoglobin level (10-11 g/dL).<sup>588</sup> On the basis of these results, an upper limit of hemoglobin target of 11.5 g/dL has been generally recommended with the use of erythropoiesis-stimulating agents.

Long-term post-heart transplant survival in patients with ESRD without kidney transplant is poor. Kidney transplant appears to improve survival; with a single-center study reporting long-term survival that is comparable to patients without ESRD.<sup>589, 590</sup> Preemptive transplantation with a living donor or extended criteria deceased donor is encouraged in this setting.<sup>591</sup>

### **BK polyomavirus**

BK polyomavirus (BKV) has been described in heart transplant recipients, although data remains limited. Viremia has been estimated at 19% and viremia at 5% in adult recipients.<sup>592</sup> Risk factors for BKV infection may include CMV infection and rejection treatment.<sup>593, 594</sup> In a single-

center study of 98 pediatric heart recipients, 34% had BK viremia, 7% had BK viremia, and one patient developed biopsy-proven BK nephropathy that progressed to ESRD<sup>595</sup>; a history of EBV infection was found to be associated with BKV infection in these children. Evaluation for BKV should be considered in patients with progressive renal dysfunction without an otherwise identifiable cause. Management is modeled after the kidney transplant population and generally involves decreasing immunosuppression while carefully monitoring for rejection as the primary approach. Several antiviral therapies have been used to treat BK nephropathy, including cidofovir, leflunomide, fluoroquinolones, and IVIG, but none has been systematically studied or approved for the treatment of BK nephropathy.<sup>596, 597</sup>

### **Additional pediatric perspective**

Despite the general lack of co-morbidities compared to their adult counterparts, there are several factors that influence kidney outcomes in the pediatric population. In pediatric heart transplant recipients suffering from end-stage heart failure, VAD support improves renal function, but patients with a lower pre-VAD eGFR and those that do not have normalization of renal function in response to VAD support are at higher risk for development of CKD after transplant.<sup>598, 599</sup> In a single center study by Williams et al, 67% of non-renal pediatric solid organ transplant recipients suffered an episode of perioperative acute kidney injury (AKI), which was a risk factor for progression to CKD.<sup>600</sup> Similar to adult heart recipients, CNI maintenance immunosuppression contributes to the development of CKD. African-American race, a history of hemodynamically significant rejection, and decreased eGFR at 1-year post-transplant are risk factors for late CKD in pediatric recipients.<sup>601</sup> ESRD occurs in 4% of pediatric heart recipients, with a risk of 3% at 10 years and 16% at 20 years.<sup>602</sup> Risk factors for the development of ESRD in children include age at heart transplant > 1 year, African American race, older era (transplant before 2000), hypertension, diabetes, re-transplant, acute dialysis, graft failure, and hospitalized infection.

## Topic 5. Chronic Kidney Disease After Heart Transplantation

### 2010 Prior Guideline Recommendation

Estimation of GFR with the 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<sup>2</sup>, and/or fast GFR decline in the past (> 4 mL/min/1.73 m<sup>2</sup> per year).

Class I, Level of Evidence: C

### 2023 Guideline Update Recommendation

In HT recipients, renal function should be assessed at least twice a year, including estimation of GFR and assessment of albuminuria to identify CKD. The CKD-EPI or the MDRD equations should be used to estimate GFR in adults. In children, GFR can be estimated by the modified Schwartz formula. Where available, GFR may also be estimated from serum Cystatin C.

**Class I, Level of Evidence: C**

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## Topic 5. Chronic Kidney Disease After Heart Transplantation

## 2010 Prior Guideline Recommendation

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. (Class I, Level of Evidence: C)

HT recipients with an estimated GFR < 30 mL/min/1.73m<sup>2</sup>, proteinuria > 500 mg/day (or urine albumin/creatinine ratio > 500 mg/g), or rapidly declining GFR (> 4 mL/min/1.73 m<sup>2</sup> per year), should be referred to a nephrologist for management of metabolic abnormalities and other complications of renal insufficiency and consideration of renal transplantation.

Class I, Level of Evidence: C

In all HT recipients (adult and pediatric) with 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. (Class I, Level of Evidence: B)

Due to the potential for precipitating rejection, CNI free regimens should be used with caution in HT recipients with significant renal insufficiency which persists despite CNI reduction. (Class I, Level of Evidence: C)

In pediatric HT recipients, CS minimization or withdrawal should be attempted to avoid hypertension and subsequent CKD, as long as there is no clinical rejection. There is no strong data in adult HT recipients. (Class I, Level of Evidence: B)

Interventions that have been proven to slow the progression of CKD in the general population should be considered in all HT recipients. These include strict glucose and blood pressure control and use of an ACEI or angiotensin receptor blocker (ARB). The American Diabetes Association 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.

Class I, Level of Evidence: C

In pediatric HT recipients, diabetes is rare. In contrast hypertension is common and adequate blood pressure control with a calcium channel blocker or ACEI is warranted to avoid CKD. (Class I, Level of Evidence: C)

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

Class I, Level of Evidence: C

## 2023 Guideline Update Recommendation

**Recommendation removed: combined with the above.**

HT recipients with CKD should be referred to a nephrologist for management of metabolic abnormalities and other complications of renal insufficiency and consideration of renal replacement therapy if: i.

estimated GFR < 30 mL/min/1.73 m<sup>2</sup>. ii.

significant albuminuria, defined as urinary albumin creatinine ratio ≥ 300 mg/g (or ≥ 30 mg/mmol or albumin excretion rate ≥ 300 mg/24 hours), approximately equivalent to protein creatinine ratio ≥ 500mg/g (or ≥ 50 mg/mmol or protein excretion rate > 500 mg/day). iii.

Rapidly declining GFR (>5mL/min/1.73 m<sup>2</sup> per year).

(from Kidney Disease: Improving Global Outcomes Consensus Conference [KDIGO] guidelines<sup>583</sup>)

**Class I, Level of Evidence: C**

**Recommendation removed: CNI minimization and withdrawal covered in Topic 1.**

**Recommendation removed: see updates covered in Topic 1.**

**Recommendation removed: see updates covered in Topic 1.**

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 control and blood pressure control with use of an ACEI or ARB, and SGLT2 inhibition for those with diabetes and CKD. Diabetes and blood pressure should be managed according to contemporary guidelines with consideration given to the importance of concomitant cardiovascular risk factors.

**Class I; Level of Evidence: C**

**Recommendation removed.**

Hemoglobin (Hgb) levels should be measured at least annually in HT patients with CKD to exclude anemia (Hgb < 13 g/dL in adult males, Hgb < 12 g/dL in adult females). In patients with CKD post-HT, work-up for anemia should include assessment of secondary causes including iron deficiency. In patients with iron deficiency anemia, initial therapy and routes of administration should be determined by clinicians, patient preferences, and local available resources. However, erythropoiesis-stimulating agents should not be used to increase Hgb levels >11.5 g/dL.

**Class I; Level of Evidence: C**

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*(Continued)***Topic 5. Chronic Kidney Disease After Heart Transplantation****2010 Prior Guideline Recommendation**

Kidney transplantation should be considered the treatment of choice for all HT recipients (adult and pediatric) with endstage renal disease who are appropriate candidates. Living donation should be considered. (Class I, Level of Evidence: C)

Calcium channel blockers should be considered the antihypertensive drug of choice when optimal blood pressure control cannot be achieved with ACEI/ARB, or when these drugs are contraindicated in HT recipients. (Class II, Level of Evidence: C)

**2023 Guideline Update Recommendation**

**Recommendation removed: updates added to new Topic 11 which includes multiorgan transplant**

**Recommendation removed: added to Topic 6, Hypertension section.**

**Topic 6: Management of cardiovascular risk after heart transplantation****Diabetes**

Monitoring and management of diabetes in heart transplant recipients is performed similarly to the general population.<sup>603</sup> Metformin remains an excellent agent in patients without advanced renal failure, especially in light of recent evidence suggesting lower rates of vasculopathy and post-transplant malignancy.<sup>604, 605</sup> Sodium-glucose transport protein 2 (SGLT2) and glucagon-like peptide 1 receptor agonists (GLP-1RA) inhibitors have proven effective in reducing major cardiovascular and renal events in patients with diabetes.<sup>606, 607</sup> Additional evidence demonstrates that these agents reduce the risk of hospitalization or death from cardiovascular causes in patients with heart failure and a reduced ejection fraction regardless of the presence or absence of diabetes.<sup>608, 609</sup> A small series in 16 heart transplant recipients demonstrated that short-term (median 9 months) of a SGLT2 inhibitor treatment was associated with significant reductions in body weight, blood pressure, and furosemide dose; none of these changes were observed in the cohort of heart transplant patients with diabetes who were managed with non-SGLT2 inhibitor therapies at this center.<sup>610</sup> These authors also report no adverse infectious events and no significant drug-drug interactions (other than the reduction in furosemide dose).<sup>610</sup> A recent retrospective study of 21 heart transplant recipients with type-2 diabetes treated with SGLT2 inhibitors demonstrated weight loss and reductions in insulin use, hemoglobin A1c, and low-density lipoprotein cholesterol without adverse events.<sup>611</sup> Based on these limited experiences in transplant patients along with the extensive evidence for effectiveness and safety in non-transplant patients, SGLT2 inhibitors can be considered as an option to manage post-transplant diabetes mellitus in select heart transplant recipients. Replication of these findings in large prospective trials is required before widespread endorsement of these agents can be made in the post-transplant setting.

**Hypertlipidemia**

Statins extend life and reduce rates of cardiovascular events in heart transplant recipients; however, interactions with

immunosuppressant medications (particularly CNIs) can limit dose titration or lead to intolerance of this vital drug class. Extensive data in nontransplant patients support the benefits of aggressive LDL lowering in reducing residual cardiovascular disease burden, and recent evidence in heart transplant recipients suggests that aggressive and early LDL management can mitigate CAV risk.<sup>612–614</sup> Although there is no evidence for a target LDL concentration in these patients, it is reasonable to aim for level below 100 mg/dL (or 2.5 mmol/L) for most patients, with more aggressive targets reserved for those with evidence of CAV.

Proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors can lower serum LDL to levels previously unobtainable with older lipid lower therapies, and can reduce residual cardiovascular disease in non-transplant patients.<sup>615</sup> Recently several small reports have demonstrated that PCSK9 inhibitors can safely lower LDL in heart transplant patients without interacting with key immunosuppressant medications.<sup>616–620</sup> While this initial success in heart transplant patients is encouraging, these series are limited by short-term therapy, and only one study has reported angiographic follow-up.<sup>621</sup> Nevertheless, in light of this positive initial data in transplant patients combined with the overwhelming safety and efficacy data in nontransplant recipients, PCSK9 inhibitors are reasonable adjuncts to statins in adult heart transplant patients with uncontrolled hyperlipidemia or as alternative agents in the setting of statin intolerance. Data in children is extremely limited with one randomized study of evolocumab that included children  $\geq 12$  years,<sup>622</sup> and one ongoing clinical trial assessing efficacy, safety, and tolerability of this drug in children heterozygous for familial hypercholesterolemia ages 10 to 17 years.<sup>623</sup>

Ezetimibe can produce modest decreases in serum LDL and can reduce residual cardiovascular risk when combined with a statin in nontransplant patient populations. This agent has proven effective in managing hyperlipidemia after heart transplant without affecting immunosuppressive drug levels.<sup>620, 624</sup> As such ezetimibe can also be considered as adjuncts to statins in adult heart transplant patients with uncontrolled hyperlipidemia or as alternative agents in the setting of statin intolerance. There is limited experience using ezetimibe in children aged 10 to 17 years with genetic hyperlipidemias.<sup>625</sup>

## Hypertension

Hypertension is common in pediatric and adult heart transplant patients, and is largely attributed to CNI therapy.<sup>445, 501, 626</sup> Activation of the renin-angiotensin system, increased production of endothelin-1, induction of oxidative stress, and alteration of the nitric oxide system are proposed mechanisms in CNI-induced hypertension.<sup>626, 627</sup> A recent large randomized study of the general population at high cardiovascular risk, demonstrated that intensive treatment of systolic blood pressure targeting 120 mm Hg resulted in improved survival when compared to standard treatment targeting 140 mm Hg.<sup>628</sup> While this study was not specific to the heart transplant population, CAV is so prevalent in the heart transplant population that it is reasonable to recommend aggressive hypertension treatment when other cardiovascular risk factors are also present (e.g., history of ischemic cardiovascular disease, history of smoking, hyperlipemia, obesity, diabetes, etc.). Angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor

blockers (ARB), and calcium channel blockers generally represent first-line therapy, especially for those patients with diabetes.<sup>629, 630</sup> However, there is increasing evidence that thiazide-based diuretics may have benefit for those with CNI-induced hypertension.<sup>631</sup>

## Aspirin use

There are no randomized studies analyzing the effect of antiplatelet therapy with aspirin in heart transplant recipients as primary prevention for cardiovascular events. However, two recent observational studies suggest use of early aspirin (first year post-transplant) is associated with lower CAV development and a lower incidence of CAV-related events in adult heart transplant recipients.<sup>632, 633</sup> In addition, the Early Initiation of Antiplatelet Therapy In Heart Transplantation trial (AERIAL) will randomize patients post-transplant to placebo, aspirin, or clopidogrel.<sup>634</sup> This is a feasibility trial, but secondarily will determine the effect of early initiation of antiplatelet therapy on coronary health.

### Topic 6. Management of Cardiovascular Risk After Heart Transplantation

#### Diabetes

##### 2010 Prior Guideline Recommendation

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

Class I, Level of Evidence: C

Patients should be periodically screened for diabetes after HT by measuring fasting plasma glucose levels or with an oral glucose tolerance test (more sensitive screening test for pre-diabetic state) and HbA1c determination, as appropriate. The frequency of screening will depend on risk factors and immunosuppressive therapy.

Class I, Level of Evidence: C

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

Class I, Level of Evidence: C

HT recipients with diabetes should be counseled regarding weight control, diet/nutrition, and exercise.

Class I, Level of Evidence: C

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

Class I, Level of Evidence: C

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

Class I, Level of Evidence: C

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

##### 2023 Guideline Update Recommendation

Continuing Approval Without Change

Continuing Approval Without Change

Therapies for short-term perioperative and long-term chronic glycemic control in HT recipients should be based on contemporary guidelines.

**Class I, Level of Evidence: C**

\*HT recipients with diabetes should be counseled regarding weight control, diet/nutrition, and exercise; and annual screening should be performed for diabetic complications (ophthalmology, podiatry, peripheral vascular disease, etc.)

**Class I, Level of Evidence: C**

\*Recommendations combined into one.

Continuing approval without change

Continuing approval without change

**Recommendation removed: current updates added to the lipid section below.**

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## Topic 6. Management of Cardiovascular Risk After Heart Transplantation

## Diabetes

## 2010 Prior Guideline Recommendation

Annual screening should be performed for diabetic complications (ophthalmology, podiatry, peripheral vascular disease, etc.) in HT recipients with diabetes. (Class I, Level of Evidence: C)

An endocrinology consultation may be considered when a pre-diabetic state or diabetes is diagnosed in a HT recipient.  
Class II, Level of Evidence: C

## 2023 Guideline Update Recommendation

**Recommendation removed: combined with above recommendation.**

Continuing approval without change

## Hypertension

## 2010 Prior Guideline Recommendation

Anti-hypertensive therapy in HT recipients has benefits similar to those in the general population, therefore hypertension after HT should be treated to achieve the same goals recommended for the general population.  
Class I, Level of Evidence: C

Lifestyle modifications including weight loss, low sodium diet, and exercise are appropriate adjuncts to facilitate control of blood pressure in HT recipients. (Class I, Level of Evidence: C)

Drug choice for treatment of hypertension in HT recipients is empiric and depends on blood pressure responses. Calcium channel blockers are most widely used, but ACEI and ARB may be preferred in diabetics and a 2-drug regimen can include both calcium channel blockers and ACEI/ARB. (Class I, Level of Evidence: C)

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

Class I, Level of Evidence: C

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

Class I, Level of Evidence: C

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

Class II, Level of Evidence: C

Calcium channel blockers should be considered the antihypertensive drug of choice when optimal blood pressure control cannot be achieved with ACEI/ARB, or when these drugs are contraindicated in HT recipients.

Class II, Level of Evidence: C

## 2023 Guideline Update Recommendation

Continuing Approval Without Change

**New Combined Recommendation (with below):**

Treatment of hypertension in HT recipients should include recommendations for lifestyle modifications including weight loss, low sodium diet, and exercise in addition to drug therapy. ACEI and calcium channel blockers may be preferred as first line therapy in patients with diabetes and as a CAV prevention strategy, while hydrochlorothiazide could be considered to specifically counteract CNI-induced hypertension.

**Class I, Level of Evidence: C**

**Now combined with the above**

Continuing approval without change

Continuing approval without change

Continuing approval without change

Continuing approval without change.

Hyperlipidemia	
2010 Prior Guideline Recommendation	2023 Guideline Update Recommendation
<b>New recommendation</b>	Biannual measurements of lipid levels should be performed in adult heart transplant recipients. <b>Class I, Level of Evidence: C</b>
<b>New recommendation</b>	It is reasonable to target LDL levels below 100 mg/dL (2.5 mmol/L) in heart transplant recipients, but there must be close monitoring for potential interactions between lipid lowering therapies and immunosuppressive agents. <b>Class IIa, Level of Evidence: C</b>
<b>New recommendation</b>	Proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors and ezetimibe can be considered as adjuncts to statin therapy in heart transplant recipients with uncontrolled hyperlipidemia, or as primary therapy in those with statin intolerance. (Experience in Pediatrics is limited to $\geq 12$ years for PCSK9 and $\geq 10$ years for ezetimibe). <b>Adults: Class IIb, Level of Evidence: B</b>

Aspirin	
2010 Prior Guideline Recommendation	2023 Guideline Update Recommendation
<b>New recommendation</b>	It is reasonable to consider routine use of aspirin early after heart transplant for prevention of CAV. <b>Class IIb, Level of Evidence: C</b>

### Topic 7: Other complications of chronic immunosuppression

There have not been significant new developments since the 2010 document and complications of immunosuppressive drugs is common as previously described.<sup>635</sup>

Topic 7. Other Complications of Chronic Immunosuppression	
2010 Prior Guideline Recommendation	2023 Guideline Update Recommendation
Recommendations for addressing other complications of immunosuppression include regular screening for adverse events, minimizing drug doses, drug substitution, 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, while acquired cataracts require surgical intervention. It is important to assess for contraindications and drug interactions when medically treating complications of immunosuppression.	Continuing Approval Without Change
<b>Class I, Level of Evidence: C</b>	

### Topic 8: Arrhythmias

#### *Atrial arrhythmias and supraventricular tachycardia*

The incidence of atrial arrhythmias is variable through the course of transplant follow-up and may be as high as 30%. Atrial arrhythmias may be related to underlying CAV, acute rejection, and acute illness such as sepsis.<sup>636</sup> Therefore, endomyocardial biopsy and coronary angiography should be considered in heart transplant recipients with new-onset atrial arrhythmias. The development of atrial arrhythmias is associated with poorer post-transplant outcomes.<sup>123, 637</sup>

The majority of atrial arrhythmias are right atrial macro-reentrant atrial arrhythmias such as atrial flutter (AFL).<sup>638, 639</sup> Atrial fibrillation (AF) appears to be less common. Re-establishment of electrical connection between the recipient and donor atria is also a recognized substrate for atrial arrhythmias.<sup>640</sup> Some studies report a lower incidence of non-cavotricuspid isthmus (CTI)-dependent AFL with bicaval compared to bi-atrial anastomosis but both CTI and non-CTI-dependent AFL can occur irrespective of the surgical technique. The electrocardiographic morphology of the AFL cannot reliably determine the nature of the AFL. In the absence of acute graft rejection, electrophysiologic studies may elucidate the substrate for atrial arrhythmias. Electrical cardioversion and radiofrequency ablation may be considered in a heart transplant recipient with symptomatic and persistent atrial arrhythmias. Anticoagulation therapy should be considered in heart transplant recipients with AF or AFL to reduce the risk of systemic thromboembolism, based on conventional risk stratification schemes (e.g., CHADS-VASc score).<sup>641</sup>

Atrioventricular re-entry tachycardia (AVRT) or atrioventricular nodal re-entry tachycardia (AVNRT) are uncommon and related to an underlying electrophysiological substrate within the donor heart. Adenosine may be considered to terminate SVT in heart transplant recipients, but should only be administered with caution at low doses (e.g., 3 mg in adults) due to increased risk of severe bradycardia or asystole (refer to Task Force 1 for guideline recommendations for adenosine use in heart transplant recipients).<sup>642</sup> Symptomatic AVRT and AVNRT can be managed with radiofrequency ablation of the accessory pathway and slow pathway, respectively.

### **Ventricular arrhythmias and sudden death**

Sudden death is a well-recognized mode of death in heart transplant recipients. The variable incidence of reported sudden death is probably due to the small sample sizes of existing studies, heterogeneity in the patient populations studied, and inconsistent or unspecified definitions used. Acute rejection and CAV are major risk factors for sudden death in adult heart transplant recipients<sup>643, 644</sup>; the former accounting for the majority of sudden deaths in the early post-transplant course. In a recent analysis of the ISHLT registry, the risk of sudden death within 2 years of the diagnosis of CAV, particularly in the presence of cardiac dysfunction and prior history of acute rejection, is as high as 8%.<sup>645</sup> Other large registry studies have also identified reduced left ventricular ejection fraction (<40%) as a predictor of sudden death.<sup>646</sup> In pediatric recipients, rejection, older recipient age, black race, and non-urgent status at listing were associated with sudden death.<sup>647</sup> Ventricular arrhythmias and aborted sudden death in heart transplant recipients of any age should prompt urgent investigations including endomyocardial biopsy and coronary angiography.

Observational studies suggest that sudden death in heart transplant recipients may be related to brady- or tachyarrhythmias, secondary to ischemia, inflammation, and/or fibrosis.<sup>648</sup> One registry study showed better survival in heart transplant recipients with permanent pacemakers,<sup>119</sup>

but the clinical implications of this finding requires further study. A number of studies have also reported the outcomes of heart transplant recipients with implantable cardioverter-defibrillators (ICD), which are most commonly used in patients with CAV. Case series infer that ICD therapy may be of benefit in selected patients with severe allograft vasculopathy, unexplained syncope, and severe left ventricular dysfunction, given the high risk of associated ventricular arrhythmias.<sup>649, 650</sup> However, ICD therapy for ventricular arrhythmias is a poor surrogate for reduction in arrhythmic death, and successful termination of ventricular arrhythmias may not prevent mortality as the graft fails.<sup>651</sup>

In general, conventional indications for ICD therapy have been adopted in the absence of clinical trials of ICD therapy in heart transplant recipients.<sup>652</sup> A reduced left ventricular ejection fraction (<35%) is generally used to guide ICD therapy for primary prevention in the absence of established criteria in adult heart transplant recipients. In addition, ICD may be considered in patients with severe CAV who are being considered for re-transplantation.

### **Late bradyarrhythmia and pacemaker therapy**

There are few reports on late bradyarrhythmia and pacemaker therapy in the heart transplant population. In one single-center study, the incidence of late (>3 months post-transplant) pacemaker therapy for bradyarrhythmia was about 4.4%, with the same incidence of sinus node dysfunction and atrioventricular (AV) block.<sup>653</sup> Another group reported that AV block may be more common than sinus node disease in heart transplant patients with late bradyarrhythmias.<sup>654</sup>

Reports of the association between late bradyarrhythmias, donor age, and operative time are inconsistent.<sup>653–655</sup> Although acute rejection may result in bradyarrhythmias, late sinus node dysfunction and AV block are often not related to acute rejection.<sup>656, 657</sup> In general, conventional indications for permanent pacemakers should be applied in these patients. Reports of cardiac resynchronization therapy (CRT) in heart transplant recipients are sparse but may be considered in selected patients with impaired LV function and AV block.

Topic 8. Arrhythmias	
2010 Prior Guideline Recommendation-None	2023 Guideline Update Recommendation
<b>New recommendation</b>	Clinicians should consider endomyocardial biopsy and coronary angiography in HT recipients with atrial or ventricular arrhythmias to exclude acute rejection and assess for CAV. <b>Class I, Level of Evidence: B</b>
<b>New recommendation</b>	Clinicians should consider echocardiography in HT recipients with atrial or ventricular arrhythmias to assess cardiac function. <b>Class I, Level of Evidence: B</b>
<b>New recommendation</b>	Clinicians should consider anticoagulation therapy in HT recipients with AF/flutter to reduce the risk of systemic thromboembolism guided by CHADS-VASc score. <b>Class I, Level of Evidence: C</b>
<b>New recommendation</b>	Clinicians should consider electrophysiological evaluation in HT recipients with atrial arrhythmias or SVT to determine the nature of the arrhythmias. <b>Class I, Level of Evidence: B</b>

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## Topic 8. Arrhythmias

2010 Prior Guideline Recommendation-None

2023 Guideline Update Recommendation

**New recommendation**

Permanent pacing is recommended regardless of symptoms in HT recipients with second-degree Mobitz type II atrioventricular block, high-grade atrioventricular block, or third-degree atrioventricular block.

**Class I, Level of Evidence: B****New recommendation**

Dual chamber pacing is recommended over single chamber ventricular pacing in HT recipients with sinus node dysfunction and atrioventricular block who require permanent pacing.

**Class I, Level of Evidence: A****New recommendation**

Clinicians should consider DC cardioversion in HT recipients with sustained atrial arrhythmias or supraventricular tachycardia to restore sinus rhythm and improve symptoms.

**Class IIa, Level of Evidence: A****New recommendation**

Clinicians should consider radiofrequency ablation in HT recipients with symptomatic sustained atrial arrhythmias or supraventricular tachycardia (AT, AVRT, and AVNRT) to maintain sinus rhythm and improve symptoms.

**Class IIa, Level of Evidence: B****New recommendation**

Non-dihydropyridine calcium channel blockers and beta-blockers may be used in HT recipients with preserved ejection fraction for ventricular rate control of AF.

**Class IIa, Level of Evidence: B****New recommendation**

The Class III antiarrhythmics sotalol and amiodarone can be safely used in HT recipients for rhythm control, but close monitoring of immunosuppressive agents is recommended.

**Class IIa, Level of Evidence: C****New recommendation**

Permanent pacing is reasonable in HT recipients with marked first-degree or second-degree Mobitz type I (Wenckebach) atrioventricular block with symptoms that are attributable to the atrioventricular block.

**Class IIa, Level of Evidence: C****New recommendation**

In patients with atrioventricular block who have an indication for permanent pacing with a LVEF between 36% and 50% and are expected to require ventricular pacing more than 40% of the time, it is reasonable to choose pacing methods that maintain physiologic ventricular activation (e.g., CRT or His bundle pacing) over right ventricular pacing.

**Class IIa, Level of Evidence: B****New recommendation**

Radiofrequency ablation may be considered in HT recipients with AF to maintain sinus rhythm and improve symptoms.

**Class IIb, Level of Evidence: C****New recommendation**

In patients with a heart transplant and severe allograft vasculopathy with LV dysfunction, an ICD may be reasonable if meaningful survival of greater than 1 year is expected.

**Class IIb, Level of Evidence: C****Topic 9: Anticoagulation after heart transplant**

Direct oral anticoagulants (DOACs), when compared to a vitamin K antagonist (VKA), impart significantly lower risk of intracranial hemorrhage in patients with AF.<sup>658–660</sup>

These agents are also associated with comparable, or lower, rates of stroke and systemic embolism depending on the dose and the drug studied. Consequently recent updates to the AF guidelines advocate for DOACs as first line therapy over warfarin for eligible patients.<sup>661</sup> Similarly, based on consistent reductions in rates of major bleeding across

clinical trials, a DOAC is now preferred to a VKA for the initial and long-term treatment of venous thromboembolism (VTE) in patients without cancer.<sup>662</sup>

While DOACs possess more predictable pharmacokinetic profiles than VKAs, drug-drug interactions still exist, which is particularly salient in transplant recipients given the need for concomitant CNI therapy. Cyclosporine is a potent inhibitor of intestinal and hepatic efflux transporters including p-glycoprotein (P-gp), hepatic uptake transporters such as organic anion transporting polypeptide, and CYP3A4. Tacrolimus likewise inhibits both CYP3A4 and



P-gp, but to a lesser extent than cyclosporine.<sup>663</sup> All DOACs require P-gp for elimination, while rivaroxaban and apixaban are also substrates of CYP3A4.<sup>664</sup>

Several studies have explored various drug-drug interactions between immunosuppressants and DOACs in adult transplant patients. Wannahoff et al<sup>665</sup> evaluated nine liver transplant patients on stable maintenance immunosuppression (cyclosporine, n = 5 and tacrolimus, n = 4) and found that the mean trough concentration of rivaroxaban was 131.7 ng/mL in patients treated concomitantly with cyclosporine vs 20.3 ng/mL in patients receiving tacrolimus. Three of five patients in the cyclosporine group reported episodes of mild bleeding vs only one patient receiving tacrolimus. Conversely, Ambrosi et al<sup>666</sup> administered rivaroxaban to 11 heart transplant patients and noted that trough anti-Xa activity was less than 137 ng/mL (upper limit of the usual therapeutic range) in all patients, except one patient with severe renal impairment (creatinine clearance of 25 mL/min). Bashir et al examined the interaction between cyclosporine and tacrolimus with apixaban in 12 healthy adult male volunteers. These authors found a slight increase in apixaban C<sub>max</sub> and AUC<sub>(0-tlast)</sub> with concomitant cyclosporine and a slight reduction in apixaban C<sub>max</sub> and AUC<sub>(0-tlast)</sub> with tacrolimus; neither interaction was deemed clinically relevant.<sup>667</sup> Additionally, Vanhove et al<sup>668</sup> evaluated 39 organ recipients treated with the combination of a CNI and rivaroxaban (n = 29) or apixaban (n = 10) and found a limited (<20%) increase in CNI trough concentration with simultaneous administration. Finally, while there are no published data describing the combination of a PSI with a DOAC, simultaneous administration of these agents should not result in any appreciable change in drug exposure for either drug class.

Limited reports have described clinical outcomes with DOAC use in solid-organ transplant patients. The first published manuscript is from Lichvar et al, who evaluated 37 thoracic organ transplant patients who received a DOAC at a single center. The majority were lung (86.4%) versus heart recipients, most (86.5%) were treated for venous thromboembolism (VTE), and rivaroxaban (78.4%) was the preferred agent.<sup>669</sup> Two patients had breakthrough VTE during DOAC therapy, while 8 bleeding events were reported in the cohort. There was no difference in the incidence of bleeding in patients with and without drug-drug interactions and during DOAC therapy (26.0% vs 7.1%, *p* = 0.154), which is likely due to the frequent dose reduction for drug interaction and/or renal insufficiency seen in this cohort. A second study by Henricksen et al. was recently published, which included 73 patients, of whom 22 received warfarin and 51 received a DOAC (apixaban = 35).<sup>670</sup> Bleeding and VTE rates were low and comparable between groups. Interestingly, both patients with VTE reoccurrence were on reduced dose apixaban (2.5 mg twice daily) due to a presumed drug interaction with itraconazole. While data comparing DOACs post-transplant is sparse, one recently published single-center analysis of 106 solid-organ transplant recipients found that the cumulative incidence of any bleeding was lower in the apixaban arm compared to the non-apixaban arm at both 90 days (4.9% vs

16.1%) and 180 days (11.4% vs 24.9%, *p* = 0.034)<sup>671</sup> Finally, in addition to these published manuscripts, several abstracts describing the use DOACs in various solid-organ transplant patients have also recently been presented at national conferences, all of which reported acceptable safety and efficacy.<sup>672–676</sup>

While the safety of DOAC administration pre- and post-biopsy has not been studied in heart transplant patients, this issue of perioperative DOAC administration was recently addressed in the PAUSE trial,<sup>677</sup> which enrolled over 3,000 patients with atrial fibrillation using apixaban, dabigatran, or rivaroxaban. The DOAC regimens were omitted for 1 day before a low-bleeding-risk procedure and 2 days before a high-bleeding-risk procedure and were resumed 1 day after a low-bleeding-risk procedure and 2 to 3 days after a high-bleeding-risk procedure. Following this approach, simple procedures yielded 30-day postoperative rates of major bleeding of less than 2% and rates of stroke less than 1%.

In summary, significant evidence in nontransplant patient populations and limited evidence in transplant cohorts support the recommendation that DOACs are reasonable alternatives to a VKA in adult heart transplant recipients. Drug interactions in patients with normal clearing organ function appear to be limited, with the potential exception of concerns for the possible potentiation of rivaroxaban effects when combined with cyclosporine as described above. Pharmacokinetic data in transplant patients with clearing organ dysfunction (i.e., renal failure) do not exist, hence caution is urged in this clinical scenario. Preliminary data suggests that apixaban may be safer than other DOACs post-transplant, but additional study is needed to confirm these findings. Finally, based on the data from the PAUSE trial, which included major interventions such as open-heart surgery, endomyocardial biopsy can be safely performed provided the DOAC is held for an appropriate amount of time pre- and postprocedure.

### ***Pediatric perspective***

In June 2021, the FDA approved dabigatran for the treatment of VTE in children aged 3 months to less than 12 years, making this the first oral anticoagulant approved for use in children. FDA approval was primarily based on the dabigatran etexilate for the treatment of acute venous thromboembolism in children study (DIVERSITY), which was an open label phase 2b/3 study that included 267 pediatric subjects.<sup>678</sup> This study demonstrated non-inferiority to standard of care in terms of efficacy for the treatment of VTE in children. Rivaroxaban was studied in 520 children with VTE, and again treatment with rivaroxaban was associated with low recurrence risk of thrombus and lower thrombotic burden without increased risk of bleeding compared to standard anticoagulants.<sup>679</sup> There are ongoing studies of apixaban in children with congenital or acquired heart disease<sup>680</sup> and edoxaban in children with VTE.<sup>681</sup> Future study of DOACs in pediatric HT patients specifically are needed in order to understand drug interactions and adverse reactions in this unique population.

## Topic 9. Anticoagulation

2010 Prior Guideline  
Recommendation-None

2023 Guideline Update Recommendation

**New recommendation**

The direct-acting oral anticoagulants (DOACs) can be considered as an alternative to a vitamin-K antagonist (VKA) for prophylaxis of stroke in patients who develop atrial fibrillation after heart transplant and who are receiving a tacrolimus- or PSI-based immunosuppressive regimen.

**Class IIa, Level of Evidence: B****New recommendation**

DOACs can be considered as an alternative to a VKA for the treatment of venous thromboembolism in patients after heart transplant who are receiving a tacrolimus- or PSI-based immunosuppressive regimen.

**Class IIa, Level of Evidence: B****New recommendation**

Endomyocardial biopsy can be completed in a patient receiving a DOAC provided that the anticoagulant is held at least 48 hours before procedure.

**Class IIa, Level of Evidence: B****New recommendation**

DOACs should be prescribed cautiously to heart transplant patients receiving cyclosporine-based immunosuppression regimen and in those with advanced kidney disease due to the potential for drug-drug interaction and suprathreshold DOAC exposure, respectively.

**Class IIb, Level of Evidence: B**

## Topic 10: Monitoring recipients of organs from donors at higher risk of infectious diseases

### *Recipients of organs from donors with bloodborne viral infections*

*Increased infectious risk donors.* Transmission of human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV) by organ transplantation is a rare event but with serious and potentially fatal consequences for affected recipients.<sup>682</sup> These rare, unexpected events have occurred due to failure of laboratory detection of infection in donors, most often because of recent donor infection before the antibodies and/or virus is detected in the bloodstream (also called the window period for virus detection).<sup>683</sup> Since 1994 and updated in 2013 and 2020, the United States Public Health Service (PHS) has published guidelines to reduce unintended viral transmissions by identification of donors who are at increased risk for recent infection using behavioral and medical factors. According to these guidelines, donors should be considered at risk for HIV, HCV or HBV infections if one of the following risk criteria exists during the 30 days before organ procurement when NAT-screening is performed prospectively (Table 12).<sup>684</sup>

Accompanying the guidelines to prevent unintended transmission events, in the United States, there are also Organ Procurement and Transplant Network (OPTN) policy driven mandates<sup>685</sup> to (1) provide informed consent of recipients with increased infection risk organ offers, including discussion of the risk of donor infection versus potential risks associated with declining the offer, and (2) perform post-transplant surveillance of recipients for HIV, HCV and HBV infections, with both serologic and nucleic acid testing (NAT).<sup>686, 687</sup> European and Australian authorities have introduced similar policies.<sup>688, 689</sup>

With universal viral screening of donors by both serologic and nucleic acid testing, the risk of donor infection is now better defined. Adding NAT to donor screening reduces the limit of HIV detection from 17-22 days to 5-6 days, HCV from 70 days to 3-5 days, and HBV from 35-44 days to 20-22 days.<sup>690</sup> Furthermore, models have estimated that the risk of undiagnosed viral infection is < 1/1,000,000 for HIV if the NAT testing of donors is negative at least 6.6 days (95% CI: 6.5–6.7 days) after the most recent possible exposure. The risk is < 1/1,000,000 for undiagnosed HCV if donor NAT testing is negative 12.2 days (95% CI: 12.2–12.2 days) after infection with 1 HCV virion.<sup>691</sup>

Multiple studies have demonstrated that infection risk donor organs, including heart, can be utilized safely with good post-transplant outcomes.<sup>692–694</sup> However, transmissions of HCV continue to occur, especially from donors

**Table 12** Behavioral, Social, Medical, and Other Factors That Increase Risk for Recent HIV, HBV, or HCV Infection in Organ Donors

Sex (i.e., any method of sexual contact, including vaginal, anal, and oral) with a person known or suspected to have HIV, HBV, or HCV infection
Man who has had sex with another man
Sex in exchange for money or drugs
Sex with a person who had sex in exchange for money or drugs
Drug injection for nonmedical reasons
Sex with a person who injected drugs for nonmedical reasons
Incarceration (confinement in jail, prison, or juvenile correction facility) for ≥72 consecutive hours
Child breastfed by a mother with HIV infection
Child born to a mother with HIV, HBV, or HCV infection
Unknown medical or social history

with a history of intravenous drug use (IDU).<sup>695, 696</sup> The impact of this HCV infection transmission may be mitigated by the availability of highly effective oral curative therapies for HCV infection.<sup>697</sup>

Approximately 26% of organ donors in the United States meet criteria for increased infection risk likely fueled by the ongoing opioid epidemic.<sup>698, 699</sup> While PHS criteria has improved the safety of donor organ allocation, many centers continue to underutilize such organs, including hearts, for transplantation.<sup>700, 701</sup> For this reason, the criteria by which infection risk donors are defined is undergoing further scrutiny in efforts to optimize expansion of the donor pool without sacrificing safety.

### **Donors with hepatitis B infection**

Donors with active HBV infection, defined by the presence of serum hepatitis B surface antigen (HBsAg), may transmit the infection to a recipient, although the risk is lower in immune recipients (hepatitis B surface antibody+, HBsAb+). Experience with utilization of these organs is limited to Asia and Europe<sup>702, 703</sup> due to high endemic rates of infection; in the U.S., HBsAg+ donor hearts are typically not utilized. Recipients of HBsAg+ hearts require prophylaxis with a potent antiviral such as lamivudine, tenofovir, or entecavir, and hepatitis B immune globulin is administered regardless of the immune status of the recipient (HBsAb negative or positive). The duration of antiviral prophylaxis is not well defined and is still a matter of controversy. All recipients of HBsAg+ hearts require post-transplant monitoring for HBV infection with HBV nucleic acid and HBsAg testing.<sup>704</sup>

In donor screening, the presence of hepatitis B core antibody (HBcAb) with negative HBsAg may reflect resolved infection, occult chronic infection, resolving acute infection, or false-positive assay result. This is a common scenario in organ donors, occurring in up to 4.8% U.S., 10% Spanish, 15% Italian, and 50% Asian donors.<sup>705, 706</sup> The risk of HBV transmission from HBcAb+ heart donors is negligible.<sup>707–709</sup> Risk of transmission is further mitigated by pretransplant hepatitis B immunization of waiting transplant candidates in heart recipients without demonstrated immunity. All recipients of HBcAb+ organs should undergo post-transplant surveillance for HBV infection.<sup>704</sup>

### **Donors with hepatitis C infection**

Only a small fraction of heart transplant donors is HCV seropositive. A study of the Scientific Registry of Transplant Recipients (SRTR) data showed that 2.4% of evaluable heart transplants performed from 1994 to 2003 were with HCV+ organs. In this study, transplantation of HCV seropositive donor hearts was associated with increased mortality at 1, 5, and 10 years, and this finding was independent of recipient's HCV serostatus and age. Recipients of HCV seropositive hearts were more likely to die of liver disease and coronary vasculopathy.<sup>710</sup>

The availability of direct-acting antiviral agents (DAA) for the treatment of HCV infection has resulted in a

profound shift in the approach to the management of this infection. These changes effectively altered the framework by which patients with end stage organ disease are managed and receive organ transplants. In a recent study describing the use of HCV antibody (+), HCV-RNA negative donors, there was no evidence of viral transmission during early follow-up of 14 consecutive recipients of HCV Ab+/HCV-RNA negative hearts. In the same study, an analysis of the UNOS database estimated that widespread acceptance of such organs could increase the number of heart transplants by close to 100 annually in the U.S.<sup>711</sup> In addition, the high level of safety and efficacy of DAAs in patients with chronic HCV infection provides the opportunity to explore their use in the setting of transplanting organs from HCV-viremic donors into non-HCV-viremic recipients. Trials using thoracic organs from HCV-viremic donors have recently been reported in heart and lung transplant recipients with excellent results.<sup>712–714</sup> Increasing numbers of successful outcomes in single-center studies provide support for further research with larger scale multicenter trials.<sup>715</sup> These are exciting times for the field of transplantation, since the ability to utilize HCV-positive donor organs may substantially increase the donor pool and thus increase access to organs for patients who might otherwise have died while waiting.<sup>716</sup> The risk of developing CAV in heart recipients because of the endothelial damage induced by chronic HCV infection in the donor is in fact currently unknown and requires long term data.

While uncommon, hepatitis C virus antibody positive and hepatitis B virus core antibody positive donors have been used safely in the pediatric population.<sup>717</sup> The HCV DAA drugs currently only have safety data in patients over 12 years of age, but pediatric safety studies are currently being performed.

### **Donors with HIV infection**

Heart transplantation is gaining acceptance as an advanced therapy for heart failure patients with HIV infection. Accumulating evidence from retrospective series and registry-based analyses indicate outcomes that are comparable to the general heart transplant population.<sup>718, 719</sup> With the adoption of the Human Immunodeficiency Virus Organ Policy Equity (HOPE) Act (42 U.S.C. § 274f-5(b)), select U.S. and European centers have joined South Africa<sup>720</sup> in utilizing HIV positive donor organs for abdominal organ transplantation of HIV+ recipients in a research setting, with promising preliminary results. In the United States, it is expected that the HOPE Act variance (Policy 15.7: Open Variance for the Recovery and Transplantation of Organs from HIV Positive Donors) will be expanded to include other HIV+ organs, including heart. The benefits of HIV+ donor organ utilization, including expansion of the donor pool for HIV+ persons and reduction in discarded organs, must be balanced against the potential risks of HIV superinfection (including strains with antiretroviral-resistant strains or CXCR4 tropism), and unintended transmission of opportunistic pathogens.<sup>721</sup> Longer term outcomes of such an approach are unknown.

### Donors with positive serology for *Toxoplasma gondii*

Toxoplasmosis is a rare but potentially lethal infection in SOT recipients. Heart transplant recipients are known to be at risk for toxoplasmosis, especially when recipients are seronegative and receive a heart transplant, containing tissue cysts, from a *T. gondii* infected donor.<sup>722</sup> Conflicting data have been reported about the effect of *Toxoplasma* serostatus on mortality after heart transplantation,<sup>723–725</sup> therefore it is unclear whether *Toxoplasma* serostatus impacts mortality after heart transplantation.

A variety of serologic methods can be used to detect *T. gondii* infection, most of which detect the presence of IgM and IgG antibody with varying sensitivity and specificity.<sup>726</sup> *Toxoplasma* IgG donor screening is now mandated by UNOS/OPTN policy.<sup>685</sup> Serology results in the immunocompromised transplant patient may be difficult to interpret, and polymerase chain reaction (PCR) testing can help expedite diagnosis in patients with non-specific febrile illnesses,<sup>727</sup> especially those known to be at increased risk due to discordant donor/recipient toxoplasma IgG status and inability to tolerate TMP/SMX prophylaxis. PCR is more sensitive than antibody profiling for the detection of acute infection and can be performed on all body fluids.

*Toxoplasma* donor+/recipient– (D+/R–) heart transplant recipients are at increased risk of infection. These recipients should receive targeted prophylaxis starting early post-transplant, which is generally the time of maximal immunosuppression when the majority of transmissions occur. Standard TMP/SMX pneumocystis prophylaxis regimens (TMP 160 mg/SMX 800 mg orally three times weekly or TMP 80 mg/SMX 400 mg orally daily) is likely to be efficacious in preventing post-transplant infection. Since heart transplant recipients are at increased risk, some centers recommend that D+/R– heart recipients be treated with six weeks of pyrimethamine in addition to standard TMP/SMX prophylaxis,<sup>728, 729</sup> while other centers report no increased risk of infection with TMP/SMX alone.<sup>730</sup> However, updated guidelines from the AST Infectious Disease Community of Practice suggest lifelong prophylaxis in high risk (D+/R–) heart transplant recipients.<sup>731</sup> If prophylaxis is discontinued close clinical monitoring should be instituted.

### Donors and recipients with Chagas disease

*Trypanosoma cruzi*, the parasite responsible for Chagas disease or American trypanosomiasis, has a predilection for muscle, heart and neurological cells. Screening is important

for residents of, immigrants from or travelers to endemic areas (21 Latin/South America countries). International immigration has expanded the impact of Chagas disease worldwide, with over 300,000 infected persons estimated to be living in the United States and over 80,000 in Europe.<sup>732, 733</sup>

Due to the common vertical route of transmission in endemic areas, donors whose mothers are at risk for Chagas disease should also be tested. Asymptomatic parasitemia is more common than symptomatic disease in potential donors.<sup>731, 734</sup>

Antibodies against *Trypanosoma cruzi* indicate previous exposure and current infection, unless treated. Acute parasitemia may be detected by PCR and Strout test (microscopy of blood after blood concentration), but these are generally not sufficiently sensitive for screening of organ donors because of intermittent parasitemia. For screening purposes, serology with validated antibody assays must be used.

### Donors with fungal infection

Fungal infections due to opportunistic molds or yeasts can be transmitted with an allograft. However, epidemiologic and clinical characteristics of donor-derived fungal infections in transplant recipients are poorly understood. Therefore, awareness of situations where these infections are likely in the donor is important. Most cases of donor-derived candidiasis have occurred in kidney transplant recipients in whom contaminated preservation fluid is a commonly proposed source. Donors with cryptococcal disease, including those with unrecognized cryptococcal meningoencephalitis may transmit the infection with the allograft. Active histoplasmosis or undiagnosed and presumably asymptomatic infection in the donor that had not resolved by the time of organ donation can result in donor-derived histoplasmosis in the recipient. The use of organ donors from areas endemic for coccidioidomycosis may lead to transmission of this fungal pathogen to organ recipients. Clinicians should maintain a high index of suspicion for disseminated coccidioidomycosis in patients who received organs from donors with a history of residing in endemic regions for *Coccidioides*. Transmission of filamentous fungi through organ donation, although infrequent, occurs under unique clinical and epidemiological circumstances. Donor derived risk factors associated with these infections include donor immunosuppressive state, transplant tourism practices, and in rare instances near-drowning events in the donor.<sup>735, 736</sup> Targeted treatment of suspected or documented infection in the recipient due to aforementioned pathogens is recommended.

#### Topic 10. Monitoring Recipients of Organs from Donors at Higher Risk of Infectious Diseases

2010 Prior Guideline  
Recommendation=None

2023 Guideline Update Recommendation

#### New recommendation

Recipients of organs from increased risk donors should undergo screening by serology and nucleic acid testing for HIV, HBV, and HCV 2 to 8 weeks after transplantation.

**Class I, Level of Evidence: B**

(continued on next page)

*(Continued)*

## Topic 10. Monitoring Recipients of Organs from Donors at Higher Risk of Infectious Diseases

2010 Prior Guideline  
Recommendation-None

2023 Guideline Update Recommendation

<b>New recommendation</b>	Hepatitis B core antibody positive (anti-HBc+) donor organs are generally safe for transplantation, but recipients will require monitoring of HBsAg and HBV-DNA at 2 to 8 weeks after transplantation and for liver recipients at 11 to 14 months post-transplantation. <b>Class I, Level of Evidence: B</b>
<b>New recommendation</b>	Antiviral prophylaxis is not recommended for recipients of hepatitis B core antibody positive (anti-HBc+) donors if the recipient has natural (anti-HBc+, anti-HBs+) or vaccine (anti-HBc-, anti-HBs+) immunity. <b>Class I, Level of Evidence: B</b>
<b>New recommendation</b>	All donors and recipients should be screened with IgG for Toxoplasma and this information should be used to identify patients at high risk (D+/R-). <b>Class I, Level of Evidence: B</b>
<b>New recommendation</b>	Toxoplasma D+/R- heart transplant recipients should receive targeted prophylaxis early post-transplant. Standard one-year TMP/SMX pneumocystis prophylaxis regimens (TMP 160 mg/SMX 800 mg orally three times weekly or TMP 80 mg/SMX 400 mg orally daily) is recommended. Lifelong prophylaxis may be considered. <b>Class I, Level of Evidence: B</b>
<b>New recommendation</b>	Prospective clinical and laboratory monitoring of transplant recipients at risk of Chagas transmission from an infected donor or reactivation of chronic or indeterminate Chagas post-transplant is recommended. Molecular testing using PCR methodology should be utilized whenever possible as it is a more sensitive assay modality for the identification of early disease. Tests should be performed weekly for the first 2 months post-transplant, every 2 weeks in the third month, and then monthly for at least 6 months. <b>Class I, Level of Evidence: C</b>
<b>New recommendation</b>	Recipients with suspected donor-derived cryptococcosis should have serum and CSF cryptococcal antigen testing and cultures of blood, urine, and other specimens from clinically infected sites. <b>Class I, Level of Evidence: C</b>
<b>New recommendation</b>	If histoplasmosis is the cause of death in the deceased donor or if cultures or antigen tests are positive, the transplant recipient should be prophylactically treated with itraconazole for 1 year to prevent possible disseminated histoplasmosis. Monitoring of recipients with antigenemia and antigenuria at 3-month intervals during treatment and for 1 year after stopping treatment may be considered. <b>Class I, Level of Evidence: C</b>
<b>New recommendation</b>	The use of HBsAg+ donor hearts should be limited to carefully selected, consented recipients with appropriate post-transplant antiviral treatment and monitoring of HBsAg and HBV-DNA should be serially performed for the first year after transplantation. <b>Class IIa, Level of Evidence: B</b>
<b>New recommendation</b>	Toxoplasma prophylaxis with a regimen of dapsone 50 mg daily, plus pyrimethamine 50 mg weekly plus folinic acid 10 mg weekly can be considered in sulfa-allergic patients after checking for glucose 6 phosphate dehydrogenase deficiency. <b>Class IIa, Level of Evidence: C</b>
<b>New recommendation</b>	Lifelong Toxoplasma prophylaxis is recommended in high-risk (D+/R-) heart recipients. If prophylaxis is discontinued, ongoing clinical monitoring is recommended with expedited Toxoplasma PCR testing and empiric therapy initiation for signs and symptoms of infection. <b>Class IIa, Level of Evidence: C</b>
<b>New recommendation</b>	Antiviral prophylaxis with lamivudine might be considered for up to 1 year in recipients of anti-HBc+ donors who lack HBV immunity (anti-HBc- and anti-HBs-). <b>Class IIb, Level of Evidence: C</b>

## Topic 11: Graft failure and considerations for cardiac retransplantation

In some cases, transplant professionals are tasked to consider when a patient is eligible for a second, or even third, heart transplant. This is particularly relevant in the case of pediatric heart transplant recipients who may require retransplantation very early in the lifespan. Heart retransplantation now accounts for 2 to 3% of transplants reported to the ISHLT Registries over the last decade.<sup>445, 501</sup> While retransplantation has repeatedly been identified as a risk factor for worse allograft survival compared to non-ischemic dilated cardiomyopathy, several focused analyses in this area have demonstrated this risk is mostly related to selection of retransplant candidates with multiple co-morbidities<sup>737–740</sup>; This is particularly true in the case of retransplantation for primary graft failure.<sup>741</sup> Recipients with primary graft failure are often times quite ill, frequently are supported on ECMO, and have poor renal and hepatic function at the time of listing.<sup>739</sup> The data clearly demonstrate that retransplantation is not an appropriate salvage strategy for primary graft failure, however for patients who can be stabilized with medical therapy or MCS, retransplantation can be considered in carefully selected patients with similar outcomes to primary transplantation.<sup>742, 743</sup>

Retransplantation is now a well-established therapy for select patients with CAV with adjusted outcomes similar for primary transplantation. However, the prognosis of patients diagnosed with CAV has improved over time with the use of multiple interventions to slow the progress of CAV including the use of PSIs, drug-eluting stents, and statin therapy.<sup>555</sup> A recent analysis demonstrated that in many cases medical management of patients with CAV can offer similar outcomes to retransplantation, however retransplantation was shown to offer superior outcomes in those with CAV and systolic dysfunction.<sup>744</sup> Based on this data, we have revised the recommendations for retransplantation to utilize the ISHLT CAV grading system and focus the indications for retransplantation in the case of CAV.

Retransplantation should be discussed with pediatric heart transplant candidates and/or their parents during the heart transplant evaluation process.<sup>745</sup> Discussion and education about retransplantation should occur in a developmentally appropriate manner during the follow-up care of all pediatric recipients, and should be considered as part of a structured plan to safely transition to adult heart transplant care.<sup>746</sup> Barriers to open prognostic discussion include patient/parent anxiety, parents preferring that difficult medical information not be discussed with their child, and lack of retention of prognostic information that had previously been communicated.<sup>746</sup> Despite these barriers, a large majority of adolescents and young adults wish to be involved in decision making regarding transplant and end-of-life care. Families often believe that it is the responsibility of the transplant physician to initiate these discussions.<sup>746</sup> All potential heart transplant candidates should be prepared that evaluation for retransplantation will assess for

patient specific risk factors including, but not limited to, adherence to antirejection therapy, renal function, hepatic function, diabetes mellitus, rejection history, and presence of anti-HLA antibodies.

### *Treatment of symptomatic heart failure after heart transplantation*

All heart transplant patients presenting with new onset heart failure should be evaluated for acute cellular and antibody mediated rejection and new or progressive CAV should be considered. Concurrent evaluation for CAV is particularly relevant if an acute coronary syndrome is present. New onset diastolic heart failure late (>10 years) after heart transplant can be due to CAV, chronic rejection, and allograft fibrosis without a clear history of rejection.<sup>747</sup> AMR is increasingly recognized as a contributor to late allograft failure and should be considered in the differential diagnosis.<sup>748</sup>

Symptomatic heart failure should be treated to minimize patient symptoms and maximize quality of life. Because heart failure therapies have not been systematically studied in patients after heart transplantation, it is unclear how well the general heart failure guidelines apply to heart transplant recipients. Many patients have heart failure with preserved ejection fraction phenotype for which few drugs have a proven indication. Care must be taken to minimize exacerbation of chronic kidney disease, which is almost universally present in the heart transplant population. Early involvement of palliative care in heart transplant recipients is advisable.

In transplant recipients who do not respond to oral heart failure therapy, inotropic therapy such as milrinone and/or dopamine, have been used to provide symptomatic improvement. Evaluation for repeat heart transplantation should be considered and discussed with patients suffering from symptomatic heart failure despite maximal medical management. The use of VAD therapy for treatment of allograft failure is possible but challenging.<sup>749, 750</sup> In particular, intracorporeal LVAD devices are difficult to use due to the small size of the failing heart transplant, an increased risk of infection due to use of immunosuppression, challenging surgical approaches in a re-operative candidate, and the high incidence of right heart failure in this patient population. The total artificial heart can be considered in patients who are of sufficient size, but again experience is very limited. A primary advantage of the total artificial heart is that immunosuppressive medications can be discontinued leading to improvement in kidney function and decreased risk of infection.

### *Advanced care planning*

Advanced care planning is an integral component of care of the heart transplant recipient. Heart transplantation remains a life prolonging but imperfect therapy for end stage heart failure. Balancing optimal medical therapy with management of symptoms and quality of life is not only advised

but required in the care of heart transplant recipients to achieve optimal outcomes. Heart transplant recipients, particularly those who are younger at the time of heart transplant, want information regarding prognosis.<sup>746</sup> However, that information must be delivered with care and compassion, and too often advanced care planning discussions do not occur at all.<sup>751</sup> Recipients should be offered the opportunity to discuss prognosis and care goals on an ongoing basis as post-transplant complications can arise suddenly. There is a role for integration with palliative care teams in both the pre-transplant and post-transplant periods to better address the physical, emotional, and spiritual needs of patients.<sup>752, 753</sup>

### **Multiorgan transplantation**

The utilization of multi-organ transplantation is increasing with recipients receiving kidney, lung, liver, and other solid organ transplants in conjunction with, or subsequent to, their heart transplant. The increasing use of multiorgan transplants raises unique ethical concerns which have been extensively reviewed by the OPTN Ethics Committee.<sup>754</sup> Heart transplant recipients are at increased risk of end stage renal disease due to the combined effects of heart failure, chronic kidney disease, and CNI usage. Heart transplant recipients with Stage 4 chronic kidney disease should be referred to nephrology specialists for evaluation and discussion of prognosis and treatment. In the absence of significant heart failure, preemptive renal transplantation is a superior therapy in heart transplant recipients.<sup>755</sup> Discussion should take place between the kidney and heart

transplant teams before transplant to discuss antirejection medication regimen and goal trough levels. A primary team for management of anti-rejection therapy should be identified before kidney transplant.

Simultaneous multiorgan transplant may be reasonable in carefully selected heart transplant candidates. Those with cardiac cirrhosis, particularly those with Fontan associated liver disease, may benefit from simultaneous heart-liver transplants.<sup>756, 757</sup> Heart-kidney and heart-liver transplant recipients experience similar mortality but a lower incidence of rejection than heart transplant recipients alone.<sup>93</sup> Further research is necessary to determine if this is due to selection bias, use of different anti-rejection therapy, or immunoprotection conferred by the kidney or liver. The use of simultaneous heart-kidney transplant has increased in the last decade and demonstrates good results but has led to questions about whether the utility of kidney allografts are being used optimally in this setting.<sup>758, 759</sup> The recent development of a staged kidney after liver transplant policy has raised the question of whether a similar policy might be developed for heart transplant recipients.<sup>760</sup> Using a staged approach in heart transplant recipients could limit use of kidney transplant to those recipients who meet standardized medical criteria for kidney transplant and provide a safety net to heart transplant recipients with marginal kidney function. A consensus conference held in 2019 emphasized the importance of attempting to differentiate recoverable kidney injury due to cardiorenal syndrome from intrinsic kidney disease that may benefit from simultaneous heart-kidney transplant.<sup>761</sup>

#### Topic 11. Graft Failure and Considerations for Cardiac Replantation

##### 2010 Prior Guideline Recommendation

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

Class I, Level of Evidence: B

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

Class I, Level of Evidence: C

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

Class IIa, Level of Evidence: C

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.

Class IIa, Level of Evidence: C

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

Class IIa, Level of Evidence: B

##### **New recommendation**

##### 2023 Guideline Update Recommendation

Continuing approval without change

Continuing approval without change

\*Evaluation for retransplantation should be considered in adults and children with severe CAV and allograft dysfunction in the absence of contraindications for repeat HT.

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

**Recommendation removed: combined with above**

Continuing approval without change

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*(Continued)*

## Topic 11. Graft Failure and Considerations for Cardiac Retransplantation

## 2010 Prior Guideline Recommendation

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

Class IIb, Level of Evidence: C

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.

Class III, Level of Evidence: C

## 2023 Guideline Update Recommendation

Advanced care planning is an important part of routine post-heart transplant care and should be addressed on an annual basis.

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

**Recommendation removed: combined with above**

HT recipients with early graft failure occurring less than 6 months after HT and complicated by hemodynamic compromise are likely to have multiple co-morbidities which preclude retransplantation. Retransplantation should only be considered in carefully selected patients with early allograft failure. (Class III, Level of Evidence: B)

HT recipients with graft failure due to acute rejection (< 6 months from rejection episode) are inappropriate candidates for retransplantation.

**Class III, Level of Evidence: C**

#### Task Force 4: Long-term care of heart transplant recipients: Prevention and prophylaxis

Chair: Angela Velleca

Co-Chair: Howard Eisen

Contributing Writers: Lavanya Bellumkonda, Lara Danziger-Isakov, Fabienne Dobbels, Michelle Harkess, Daniel Kim, Haifa Lyster, Yael Peled, Zdenka Reinhardt

##### Topic 1: Frequency of routine tests and clinic visits in heart transplant recipients

Routine tests and clinic visits are crucial for the success of heart transplantation (HT). The importance of lifelong follow-up by the transplant center remains an essential and

fundamental issue. Emphasis is added on the need to reduce emergency department visits and hospitalizations.<sup>762–764</sup>

The importance of multidisciplinary team-based care is expanded to include occupational therapy, pharmacy, and expertise in transplant infectious diseases, with the Level of Evidence being upgraded.<sup>218, 765, 766</sup> Additional comments are made on the importance of informing transplant center providers in the case of pregnancy and epidemiologic exposure to contagious infectious agents. Inconsistency and wide variability of practices for rejection detection in pediatric recipients remains unchanged, although several reports have been published since the 2010 guidelines (higher Level of Evidence).<sup>278, 767, 768</sup> A recommendation for routine multi-professional dedicated clinics is added.<sup>769</sup> An example of routine tests and clinic visits schedule is added (Table 13).<sup>770–772</sup>



**Table 13** Sample\*: Follow-Up Visits and Test Schedule

Year																			1	2-5	>5					
Month																			1	15	18	21	>24	>60		
Week	1	2	3	4	5	6	7	8	10	12	16	20	24	7	8	9	10	11	12	15	18	21	>24	>60		
HT clinic visit			x	x		x		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Lab tests <sup>1</sup>			x	x		x		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
ECG			x			x		x		x			x		x			x		x		x		x		
Echo			x	x		x		x		x			x		x			x		x		x		x		
B iopsy <sup>2</sup> (Other non-invasive methods as appropriate)	x	x	x	x		x		x	x	x	x	x	x			x			x				x			
Right heart study	x			x						x									x				x		x	
Dobutamine echo/SPECT/CTA														S tarting in the fifth year – to be done every other year alternating with coronary angiography										x		x
C MV DNA <sup>3</sup>	x			x				x		x	x	x	x	x	x	x	x	x	x				x		x	
Coronary angiography																								4x		
Urine 24h protein																								x		x
Malignancy screening <sup>4</sup>																								x		x
Chest X-ray																								x		x
PSA																								x		x
PRA (DSA) <sup>5</sup>				x					x				x							x				x		x
Bone density																								x		x
CPET													x											x		x
Skin-cancer screening clinic													x									x		x		x
Endocrinology clinic													x									x		x		x
Dental exam													x									x		x		x

\*The frequency of follow-up visits for HT recipients will depend on the time from HT and the postoperative clinical course. The frequency of follow-up should be increased if complications occur, particularly in patients with challenging medical or psychosocial conditions. In addition, in view of different local availabilities of newer noninvasive modalities (e.g., Gene Expression Profiling) and the lack of evidence about the optimal timing of echocardiographic studies in HT patients, it should be noted that the frequency of follow-up visits and schedule presented in the table serve merely as an example and should be tailored to each center. Furthermore, as noninvasive modalities improve, it is likely that the need for biopsies and serial conventional angiography will be reduced accordingly.

Topic 1: Frequency of Routine Tests and Clinic Visits in Heart Transplant Recipients

2010 Prior Guideline Recommendation

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.

Class I, Level of Evidence B

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. Class I, Level of Evidence B

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 biopsies 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.

Class I, Level of Evidence C

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.

Class IIa, Level of Evidence C

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.

Class IIa, Level of Evidence C

2023 Guideline Update Recommendation

Continuing approval without change.

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 medications and changes to medications based on the results of the examinations; (3) blood work; (4) echocardiogram; (5) coronary angiography. Adjunct Intravascular imaging can be considered if expertise available, as Maximal Intimal Thickening (MIT) > 0.3 mm in the first year has been shown to have prognostic value; (6) Surveillance EMB, and noninvasive rejection monitoring [Gene Expression Profiling (Allomap), DSA, BNP and high sensitivity troponins, donor-derived cell-free DNA] (7) additional education and/or interaction with members of the multidisciplinary team.

An example of a follow-up visits and test schedule is presented in Table 13 (below).

Class I, Level of Evidence B

In infants early after heart transplantation, far fewer biopsies are performed due to the need for general anesthesia and the difficulties with venous access and biopsies manipulation in small hearts and vessels. There is no consensus regarding the frequency of EMB. Ancillary noninvasive modalities for the assessment of rejection as surrogates to EMB should be considered.

Class I, Level of Evidence B

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; (3) comorbidities requiring specialized monitoring and management; (4) need for counseling, planning and co-management for life events such as pregnancy; (5) increased management complexity in graft specific issues such as tricuspid regurgitation; (6) the need to reduce emergency department visits and hospitalizations.

Class IIa, Level of Evidence C

Follow-up for HT recipients should be provided by a multidisciplinary team, including surgeons, cardiologists, nurses, mental health and behavioral specialists, dieticians, physiotherapists, occupational therapists, pharmacists, and experts in transplant infectious diseases, among many others. Patients and caregivers should recognize that HT requires a life-long commitment to medical care.

Class IIa, Level of Evidence C

(continued on next page)

*(Continued)***Topic 1: Frequency of Routine Tests and Clinic Visits in Heart Transplant Recipients****2010 Prior Guideline Recommendation**

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

Class IIa, Level of Evidence C

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.

Class IIa, Level of Evidence C

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

Class IIa, Level of Evidence C

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.

Class IIa, Level of Evidence C

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 antibiotic, 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  $\geq 101^\circ\text{F}$  ( $38^\circ\text{C}$ ) or any unexplained fever  $\geq 100.5^\circ\text{F}$  for  $\geq 48$  hours ( $38^\circ\text{C}$ ); (6)  $\geq 2$ -pound weight gain in 1 week (i.e., 900 g or more); (7) unexplained weight loss of  $> 5$  pounds (i.e., 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.

Class I, Level of Evidence C

**2023 Guideline Update Recommendation**

Continuing approval without change.

For an uneventful recovery, follow-up visits can be 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. An example schedule for follow-up visits and testing is presented in [Table 13](#) (below).

**Class IIa, Level of Evidence C**

Continuing approval without change.

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 the HT recipient. There should be effective communication between ancillary services and the transplant center-based multidisciplinary care team to ensure that care goals are aligned and achieved.

**Class IIa, Level of Evidence C**

The transplant center should collaborate with local health professionals and educate them to 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 antibiotic, anti-fungal, or anti-viral therapy for confirmed or presumed infection; (3) hypotension or an 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  $\geq 101^\circ\text{F}$  ( $38^\circ\text{C}$ ) or any unexplained fever  $\geq 101^\circ\text{F}$  ( $38^\circ\text{C}$ ) for  $\geq 48$  hours; (6)  $\geq 2$ -pound weight gain in 1 week (i.e., 900 g or more); (7) unexplained weight loss of  $> 5$  pounds (i.e., 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; (17) suspicion/diagnosis of pregnancy; (18) epidemiologic exposure to a contagious infectious agent.

**Class I, Level of Evidence C**

**Topic 2: Prophylaxis for corticosteroid-induced bone disease**

HT recipients require lifelong immunosuppressive therapy which includes CS, a common side effect of which is osteoporosis. While there remain some gaps in evidence in the optimal pre-HT management and the role of some of the non-bisphosphonate-based regimens, the importance of personalized management and involvement of endocrinologist have been included in these recommendations. A higher T score in the lumbar spine and femoral neck before HT

lowered the risk of osteoporosis post-HT. Although gaps in evidence remain, optimization of T score before HT should be considered.<sup>773, 774</sup>

All adult and pediatric HT recipients should have the recommended daily allowance of calcium and vitamin D through optimal nutrition and supplements that meet recommendations for age. With participation in daily activity for children and weight bearing and resistance training exercises for adults.<sup>773–786</sup> Surveillance bone mineral density scan with dual x-ray absorptiometry (DXA) should be carried out within 12 months after transplant and annually

thereafter in patients receiving CS and/or bisphosphonate therapy. In pediatric patients DXA should be performed through to adulthood.<sup>775, 782, 783, 785–788</sup>

To prevent bone loss in adult HT recipients, early therapy with bisphosphonates should be considered and continued for the first year as this may reduce the fracture risk. If required in osteoporotic patients bisphosphonates can be used up to 3 years post-transplant.<sup>789–794</sup> The potential role of recombinant human parathyroid

hormone, monoclonal antibody denosumab, monoclonal antibody blocking sclerostin, romosuzumab, and hormone replacement in hypogonadal men have not been investigated in HT population.

In pediatric HT recipients, bisphosphonates should be restricted to patients with reduction in bone mass density associated with low-trauma fractures or vertebral compression and in consultation with a pediatric endocrinologist.<sup>786, 795, 796</sup>

## Topic 2: Prophylaxis for Corticosteroid-Induced Bone Disease

### 2010 Prior Guideline Recommendation 2010 "Gaps in Evidence"

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.

Class I, Level of Evidence C

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.

Class I, Level of Evidence C

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)

Class I, Level of Evidence C

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.

Class I, Level of Evidence B

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.

Class I, Level of Evidence C

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

Class I, Level of Evidence B

### 2023 Guideline Update Recommendation Moved to narrative section

All adult HT candidates should be screened for pre-existing bone disease, preferably at the time of placement on the waiting list using clinical fracture risk assessment.

In adults, baseline BMD should be obtained with a dual energy x-ray absorptiometry (DEXA) scan of the lumbar spine and femoral neck.

#### **Class I, Level of Evidence: B**

All patients on long-term immunosuppression with glucocorticoids or CNIs should have ongoing assessment of BMD.

#### **Class I, Level of Evidence, B**

Continuing approval without change

All HT candidates and recipients should have the recommended daily allowance for calcium (1,000 -1,200 mg, depending on age and menopausal status) and vitamin D (600-800 IU, or as necessary to maintain serum 25-hydroxyvitamin D levels above 20 ng/mL or 50 nmol/L).

HT recipients should have serum calcium and vitamin D levels monitored periodically.

#### **Class I, Level of Evidence C**

Regular weight-bearing and resistance training should be encouraged to increase bone density.

#### **Class I, Level of Evidence B**

Lifestyle modifications should include maintaining healthy weight balanced diet, smoking abstinence and limiting alcohol intake to 1-2 drinks a day.

#### **Class I, Level of Evidence C**

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. Surveillance dual x-ray absorptiometry (DXA) should be considered within the first year to monitor skeletal fragility baseline post-transplant with continued surveillance through to adulthood.

#### **Class I, Level of Evidence B**

Continuing approval with additional references to support recommendation.

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## Topic 2: Prophylaxis for Corticosteroid-Induced Bone Disease

## 2010 Prior Guideline Recommendation

*2010 "Gaps in Evidence"*

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.

Class I, Level of Evidence C

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

Class I, Level of Evidence B

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

Class I, Level of Evidence C

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.

Class I, Level of Evidence B

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

Class IIa, Level of Evidence C

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.

Class IIa, Level of Evidence C

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

Class IIa, Level of Evidence C

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.

Class IIb, Level of Evidence B

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

Class III, Level of Evidence: B.

## 2023 Guideline Update Recommendation

*Moved to narrative section*

After HT, it is recommended children participate in regular physical activity with daily intake of calcium and vitamin D through optimal nutrition or supplements that meet recommendations for age.

**Level of Evidence: C.**

Adult HT recipients should have individualized consideration to begin anti-resorptive therapy with bisphosphonates early after HT and continue for at least the first postoperative year to reduce bone loss.

**Class I, Level of Evidence B**

Bisphosphonate therapy in adult HT recipients for the first post-transplant year may reduce fracture risk.

**Class I, Level of Evidence B**

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**

Bisphosphonates can be used up to three years post-transplant in osteoporotic HT recipients. Long-term risk of bisphosphonates should be weighed carefully.

**Class I, Level of Evidence B**

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. The decision to commence treatment should be made in consultation with a pediatric endocrinologist.

**Class I, Level of Evidence B**

Continuing approval without change

Continuing approval without change

Continuing approval with additional references.

Continuing approval without change

Continuing approval without change

### Topic 3: Exercise, nutrition, and physical rehabilitation after heart transplantation

Routine use of cardiac rehabilitation is recommended after heart transplantation to improve exercise capacity, endothelial dysfunction, skeletal muscle function, lowers the impact of adverse effects of CS and CNI therapy, and reduces cardiovascular risk factors.<sup>797–804</sup> Importance of cardiac rehabilitation in lowering readmissions post-transplant and role of moderate-intensity and vigorous exercise on long-term cardiovascular health have been included.<sup>805–807</sup> Recommendations regarding the role of home-based cardiac

rehabilitation and hybrid cardiac rehabilitation to improve functional capacity have been made.<sup>808, 809</sup> Mobile health devices to monitor physical activity and fitness should be considered in heart transplant recipients.<sup>810</sup> Routine exercise should be encouraged in pediatric heart transplant recipients to improve exercise capacity, endurance and reduce long-term cardiovascular risk factors.<sup>811, 812</sup> Additional comments on the importance of nutritional consultation to reduce risk of hypertension, diabetes and dyslipidemia are added.<sup>813</sup> Impact of cachexia and morbid obesity on post-transplant outcomes and role of weight management are included in the recommendations.<sup>814–817</sup>

#### Topic 3: Exercise, Nutrition, and Physical Rehabilitation After Heart Transplantation

##### 2010 Prior Guideline Recommendation

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.

Class I, Level of Evidence: B

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

Class I, Level of Evidence: B

##### New Recommendation

##### New Recommendation

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

##### 2023 Guideline Update Recommendation

The routine use of cardiac rehabilitation with performance of aerobic exercise training is recommended after HT for adult and pediatric patients (2-18 years) when physically and medically able to exercise. 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.

##### Class I, Level of Evidence: B

Exercise based cardiac rehabilitation is also shown to reduce readmission rates at one year.

##### Class I, Level of Evidence: B

150 minutes per week of moderate-intensity exercise or 75 minutes per week of vigorous-intensity aerobic exercise to be encouraged for long-term cardiovascular health. Additionally, high intensity interval training (HIIT) can increase peak heart rate and aerobic power and can be considered for some post-transplant patients.

##### Class I, Level of Evidence: B

Continuing approval without change.

Home-based cardiac rehabilitation (HBCR) can be an alternative to increase access for selected clinically stable low- to moderate-risk heart transplant (HT) patients, who cannot participate in center-based cardiac rehabilitation (CBCR).

HBCR is recommended and an alternative to CBCR in HT patients, to improve functional capacity and health-related quality of life. Hybrid cardiac rehabilitation (HCR), a combination of short-term CBCR with HBCR, should be considered in HT recipients and can also be used as an alternative to CBCR, to improve functional capacity

##### Class I, Level of Evidence: B

Mobile health for assessing, promoting, and monitoring physical activity and fitness, should be considered in HT recipients

##### Class IIa, Level of Evidence B

Pediatric heart transplant recipients should be encouraged to engage in physical activity daily to reduce childhood obesity, adult-onset diabetes, systemic hypertension, and dyslipidemia, all of which have become more prevalent in the last two decades

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*(Continued)***Topic 3: Exercise, Nutrition, and Physical Rehabilitation After Heart Transplantation****2010 Prior Guideline Recommendation**

co-morbidities of the individual HT recipient.  
Class IIa, Level of Evidence C

**New Recommendation****New Recommendation****New Recommendation****2023 Guideline Update Recommendation**

and are risk factors for premature cardiovascular disease.  
**Class IIa, Level of Evidence C**

Age and developmentally appropriate exercise intervention in pediatric heart recipients can improve endurance and this aspect should be discussed with pediatric HT recipients and their parent (s). Along with providing exercise programs and diaries utilizing available electronic/online technology to capture performance and provide motivation.

**Class IIa, Level of Evidence C**

Timely nutrition assessment and intervention in pediatric heart transplant recipients may improve overall health. Because nutritional status is a potentially modifiable risk factor, the development of strategies to optimize nutritional status and maintain a healthy weight/BMI with a well-balanced diet decreases the short-term risks in the post-transplant period including diabetes, systemic hypertension, and dyslipidemia.

**Class IIa, Level of Evidence C**

Weight management strategies should be employed to ensure healthy weight and avoid cachexia and obesity. Cachexia and morbid obesity are associated with increased post-transplant mortality. Morbidly obese patients were also at higher risk of rejection. Risk of post-transplant infection is higher in the underweight patients and need for dialysis is greater in those with morbid obesity. Obesity is also associated with increased risk of hyperlipidemia and hypertension after transplant. Obesity could also affect eligibility for re-transplantation if it should become necessary.

**Class IIa, Level of Evidence B**

Nutrition and exercise programs to encourage maintenance of healthy weight pre- and post-transplant may be instituted.

**Class IIa, Level of Evidence C****Topic 4: Management of intercurrent surgery in heart transplant recipients**

The 2010 recommendations for management of intercurrent surgery in heart transplant recipients are generally unchanged with some minor additions and some new recommendations detailed in Table X. Considerations for non-oral administration of immunosuppressants are updated.<sup>818</sup> Additional comments concern the use of low-risk CMV blood products for CMV-seronegative recipients. CMV safe (leuko-reduced) and CMV IgG seronegative products are considered equivalent except for

intrauterine transfusion. Platelet units are commonly apheresed and are considered leuko-reduced. Leukocyte filters need to be applied when pooled platelets are used. Both fresh frozen plasma and cryoprecipitate have less than 1 to 5 million white blood cells per unit and are considered CMV safe by most blood centers.<sup>819–822</sup> Specific measures may minimize wound-healing complications were also discussed in this guideline.<sup>823–826</sup> In addition, special anesthetic considerations should be considered/acknowledged in the management of HT recipients (Table 14).<sup>822, 827–831</sup> The issue of perioperative steroid “stress dose” is addressed.<sup>832–834</sup>

Topic 4: Management of Intercurrent Surgery in Heart Transplant Recipients

2010 Prior Guideline Recommendation

2023 Guideline Update Recommendation

**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

**Considerations for non-oral administration of immunosuppressants:**

Intravenous cyclosporine has been associated with an anaphylactic-type reaction and should be utilized carefully. In converting from oral to intravenous administration of cyclosporine, the intravenous dose must be reduced to 25 to 33% of the oral dose either as a continuous infusion over 24 hours or as an intermittent infusion over 2-6 hours every 12 hours. Intravenous tacrolimus should be given at 10% to 33% of the oral daily dose as a continuous infusion over 24 hours or as an intermittent infusion over 4 to 6 hours every 12 hours. Sublingual administration may be considered. No consensus exists on the appropriate administration technique or the optimal dose conversion from oral to sublingual. However, it is reasonable to administer the contents of immediate release capsules sublingually at 50% to 70% of the oral dose.

Mycophenolate and azathioprine; same as the oral dose.

**Class I, Level of Evidence C**

Continuing approval without change.

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

**Class I, Level of Evidence C**

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

**Class I, Level of Evidence C**

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

**Class I, Level of Evidence C**

For many surgical procedures, prophylactic antibiotic administration may be considered. Protocols may need modification in HT recipients. Aminoglycoside antibiotics and those that are potent CYP-enzyme inhibitors, such as erythromycin and clarithromycin, are best avoided, because of the risk of worsening renal dysfunction when used in combination with CYA or TAC.

**Class I, Level of Evidence C**

When needed, blood products used in HT recipients should be leukocyte poor to decrease the risk of HLA allosensitization. For CMV-seronegative transplant recipients, low-risk CMV packed red blood cells should be available.

ABO-incompatible HT recipients require specialized blood products, which must be discussed with the transplant center prior to surgery, so that the necessary products can be prepared by the local blood bank. In emergent situations, washed type O RBCs and type AB FFP and platelets are always safe.

**Class I, Level of Evidence C**

Continuing approval without change.

Anesthesia can be safely induced if 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 highly 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

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*(Continued)***Topic 4: Management of Intercurrent Surgery in Heart Transplant Recipients****2010 Prior Guideline Recommendation**

tachyarrhythmias in HT recipients.  
 Class I, Level of Evidence C  
 Care with fluid balance is important because decreased intravascular volume will exacerbate renal dysfunction, and fluid excess may not be well tolerated by HT recipients. For major surgery, CVP monitoring may be necessary.  
 Class I, Level of Evidence C  
 Immunosuppression should not be discontinued or omitted without discussion with the HT team. However, it may be prudent to omit the dose of CNI on the morning of surgery to avoid potentiating the detrimental effect of dehydration on renal function. Thereafter, immunosuppression should be continued as normal.  
 Class I, Level of Evidence C

**New recommendation****New recommendation****2023 Guideline Update Recommendation**

Continuing approval without change.

Immunosuppression should not be discontinued or modified 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, intravenous administration (as above) of MMF and AZA should be used, with the appropriate dose adjustments for CYA or TAC; or consider sublingual TAC.

**Class I, Level of Evidence C**

For patients on Proliferation Signal Inhibitors (PSI) such as everolimus and sirolimus, it is reasonable to consider interrupting high-exposure PSI administration at least 1 month before elective surgery. It is recommended that these HT patients be switched to MMF, with CNI dose adjustment (alternatively substituted by CNI), with resumption of PSI once adequate wound healing has been achieved.

For those patients where prolonged PSI discontinuation may be problematic, such as those with significant side effects from alternative immunosuppressants, an alternative approach is to withdraw the PSI approximately 1 week before surgery and then re-initiate PSI therapy 14 to 21 days postsurgery, thus allowing for adequate wound healing.

In the event of urgent surgery, severe open wound complications, or urinary fistulas, the increased risk of impaired wound healing due to concomitant risk factors could justify the withdrawal of mTOR inhibition.

Consider minimizing or reducing the use of steroids.

**Class I, Level of Evidence B**

Individualize perioperative corticosteroid "stress dose" based upon patient's history of corticosteroid intake combined with type and duration of surgery. Considerations should include potential adverse events, namely, hyperglycemia, infection, hypertension, and poor wound healing. The use of etomidate in patients at risk for adrenal suppression and crisis should be carefully considered, given its inhibitory effect on steroid synthesis and potential acute adrenal insufficiency.

**Class I, Level of Evidence C**

**Table 14** Special Anesthetic Considerations for Intercurrent Surgery in HT Recipients

Special consideration<sup>827–831</sup>  
 Single dose of etomidate, used during induction, has been shown to decrease serum concentration of cortisol for at least 24 hours. However, this has not been shown to be clinically relevant.  
 Cyclosporine has been described as prolonging muscle relaxants; this effect has not been shown in patients on mycophenolate mofetil and tacrolimus.  
 Although the apparent higher potential for infectious complications of spinal or epidural anesthesia, limited data have not demonstrated this occurrence for regional or neuraxial procedures  
 Given the complete cardiac denervation, drugs that work on the autonomic nervous system have minimal effects on the transplanted heart.  
 Indirect-acting sympathomimetics such as ephedrine are therefore not very effective for treating hypotension and maintaining cardiac output; and ketamine may not display hemodynamic stability in heart transplant patients in extremis.  
 Direct-acting sympathetic agents, like norepinephrine, epinephrine, isoproterenol, and dopamine, are effective, although the beta-adrenergic inotropic effects are attenuated early after HT.  
 Phosphodiesterases have been shown to increase inotropy in the transplanted heart. The alpha-adrenergic response of phenylephrine is effective, but the reflex bradycardia is absent.  
 The indirect acting anticholinergics (atropine, glycopyrrolate) and anticholinesterases (neostigmine, edrophonium) have no effect on the heart rate of the cardiac allograft, and the safety of neuromuscular reversal has been demonstrated in a large-scale study with no instances of severe bradycardia or cardiac arrest.  
 The direct neuromuscular blockade Sugammadex, which directly inhibits neuromuscular blocking agents, is devoid of any direct cholinergic effects, and is a reasonable alternative in HT recipients.

**Topic 5: Reproductive health after heart transplantation**

A multidisciplinary team is important in the care of pregnant HT recipients with individualized plans commencing before conception as careful considerations include review of concomitant therapy and risk of graft dysfunction. Additional comments address paternity concerns with mycophenolate and discuss risk-benefit of changing immunosuppression in view of lacking evidence for this

recommendation. Updated guidance regarding breastfeeding has evolved into one that is cautiously optimistic for several immunosuppressants.<sup>835</sup> Emphasis should be placed on contraceptive strategies together with obtaining confidential sexual history from adults and adolescent HT recipients. Updates regarding the use of barrier methods and intrauterine devices (IUD) in HT recipients were included.<sup>836–841</sup> Level of evidence was updated for HPV vaccination.<sup>842</sup> Recommendations for erectile dysfunction remain unchanged with additional supporting data.<sup>843</sup>

Topic 5: Reproductive Health After Heart Transplantation

2010 Prior Guideline Recommendation	2023 Guideline Update Recommendation
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. Class I, Level of Evidence C	A multidisciplinary team, involving specialists in maternal and fetal medicine, cardiology and transplant medicine, anesthesia, neonatology, mental and behavioral health specialists, genetics, and is important in the care of pregnant HT recipients In case of the infertile female HT patient: HT patients who wishes to become pregnant and requires ovulation induction therapy or controlled ovarian hyperstimulation for IVF – should be carefully counselled about the major potential side effects such as Hyperstimulation Syndrome and multifetal pregnancy. A single embryo pregnancy in these cases should be the standard. <b>Class I, Level of Evidence C</b>
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. Class I, Level of Evidence C	Continuing approval without change.
Individual factors in a HT recipient who wishes to become pregnant should be considered, including the risk of acute rejection	Continuing approval without change.

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## Topic 5: Reproductive Health After Heart Transplantation

## 2010 Prior Guideline Recommendation

## 2023 Guideline Update Recommendation

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 counselled on the risks of pregnancy and pregnancy discouraged if graft dysfunction and significant CAV are expected to preclude a successful outcome.

Class I, Level of Evidence C

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

Class I, Level of Evidence C

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

Class I, Level of Evidence C

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

Class I, Level of Evidence C

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

Class I, Level of Evidence C

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

Class I, Level of Evidence C

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

Class I, Level of Evidence C

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 based on the balance of maternal and fetal risk.

Class I, Level of Evidence C

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.

Class I, Level of Evidence C

Continuing approval without change.

Continuing approval without change.

Continuing approval without change.

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

For male HT recipients, mycophenolate includes a warning that therapy needs to be discontinued 90 days before having unprotected sex (even if the patient has undergone a vasectomy). The evidence for this recommendation is lacking. Male patients should be made aware of the risks/benefits of changing immunosuppression as well as the risk of rejection.

**Class I, Level of Evidence C**

Continuing approval without change.

Continuing approval without change.

Azathioprine can be used as a substitute for MMF, but this should be decided based on the balance of maternal and fetal risk.

**Class I, Level of Evidence C**

It is considered safe to breast-feed while taking prednisolone, methylprednisolone, cyclosporine, tacrolimus, or azathioprine; however, breast-feeding should be avoided if the transplant recipient is taking mycophenolic acid products, sirolimus, everolimus, and/or belatacept due to lack of clinical information.

**Class I, Level of Evidence C**

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## Topic 5: Reproductive Health After Heart Transplantation

## 2010 Prior Guideline Recommendation

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).

Class I, Level of Evidence C

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

Class I, Level of Evidence C

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

Class I, Level of Evidence: B - R.

15. Intrauterine devices (IUD) have been generally not recommended in HT recipients and 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.

Class I, Level of Evidence C

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

Class I, Level of Evidence C

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

Class I, Level of Evidence C

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.

Class I, Level of Evidence C

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

Class I, Level of Evidence C

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

Class I, Level of Evidence C

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

## 2023 Guideline Update Recommendation

Continuing approval without change.

Continuing approval without change.

Barrier methods provide inadequate pregnancy protection and should be used as an adjunct to other methods in HT recipients. They should be recommended for sexual activity to prevent sexually transmitted infections (STI).

**Class I, Level of Evidence B-R**

Intrauterine devices (IUD) are not generally recommended for HT recipients with history of pelvic inflammatory disease, structural anomalies of the uterus, on anticoagulation, or with overall increased infection risk. However, IUDs may be considered for contraception in stable HT recipients. Additionally, IUDs do not protect against STI and should be used in conjunction with a barrier method in increased risk situation.

Patient should have consultation with gynecologist regarding risk-benefit of IUD placement.

**Class I, Level of Evidence C**

Continuing approval without change.

Continuing approval without change.

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

**Class I, Level of Evidence C**

Sexually active adolescents and adult HT recipients with multiple partners should be advised to undergo screening for STI (Hepatitis B, Hepatitis C, HIV Syphilis, Gonorrhea, Chlamydia), 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.

**Class I, Level of Evidence C**

Continuing approval without change.

The 9-valent human papillomavirus (HPV) vaccine may prevent persistent HPV infection, cervical and vulvovaginal cancer precursor lesions, and genital warts secondary to HPV types. Individuals 9-45 years should receive all 3 doses before HT if possible. There is no contraindication to administering the vaccine to women after HT, although studies have shown decreased

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## Topic 5: Reproductive Health After Heart Transplantation

## 2010 Prior Guideline Recommendation

immunogenicity or efficacy in this population.  
Class I, Level of Evidence C

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

Class I, Level of Evidence C

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

Class I, Level of Evidence C

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

Class I, Level of Evidence C

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immunogenicity with quadrivalent HPV vaccination in adult solid organ transplant recipients

**Class I, Level of Evidence: IIa**

Continuing approval without change.

Continuing approval without change.

Continuing approval without change.

## Topic 6: Psychologic issues particularly related to adherence to medical therapy and management of mood disorders in heart transplant recipients

Because of its high prevalence and negative impact on clinical outcomes, nonadherence to all medications (including, but not limited to immunosuppressants) and its influencing factors should be routinely assessed in all adult and pediatric patients at every outpatient clinic visit.<sup>424, 842–848</sup> Interventions should be tailored to individual risk-factors and discussed openly with patients and their caregivers.<sup>849–851</sup> Strategies to enhance maturity and independence are important to optimize long-term outcomes in the adolescent HT recipients.<sup>852</sup> Because of their high prevalence and association with long-term outcomes, regular screening of adherence to other lifestyle recommendations is also recommended.<sup>845, 853–855</sup> 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.<sup>844, 849, 851</sup>

Screening and management of delirium and post-traumatic stress disorder early post-transplant is

indicated.<sup>845, 856–861</sup> Moreover, given their impact on post-transplant survival, depressive symptoms should also be regularly evaluated before and during long-term follow-up of HT recipients.<sup>19, 861</sup> All patients with elevated screening scores should be referred to specialized treatment. If indicated, antidepressant medication can be prescribed, with serotonin reuptake inhibitors and new-generation anti-depressants may be the safest choice.<sup>862–864</sup> Particular attention should be given to pediatric and adolescent HT patients, because they are at a greater risk of mental health comorbidities related to the psychological and physical changes associated with puberty.<sup>769, 865–869, 499, 870</sup> Further research is needed to investigate which pharmacological and non-pharmacological interventions are most effective to treat psychological problems post-transplant.

Each HT center should closely collaborate with a specialized nurse or psychologist who can screen and monitor all HT recipients at risk for non-adherence or mood disorders,<sup>218, 861, 871, 872</sup> Investing in specialized non-medical staff may result in better transplant outcomes in the long-term, although further studies testing the efficacy of adherence-enhancing interventions are warranted.

Topic 6: Psychologic Issues Particularly Related to Adherence to Medical Therapy and Management of Mood Disorders in Heart Transplant Recipients

2010 Prior Guideline Recommendation	2023 Guideline Update Recommendation
<p>Adherence with the prescribed regimen should be routinely assessed at every HT outpatient clinic visit. Class IIa, Level of Evidence C</p> <p>Because there is currently no gold standard for adherence assessment in HT recipients, it is recommended to combine methods to increase accuracy of assessment (e.g., a combination of self-report or parent report in case of children, drug levels assessment, and clinical judgment). Class IIa, Level of Evidence C</p> <p>Attention should be given not only to adherence to the immunosuppressive regimen but also to all other health recommendations appropriate for HT recipients. Class IIa, Level of Evidence: C</p> <p>Barriers to adherence should be discussed in an open, non-threatening way during visits with HT recipients. Class IIa, Level of Evidence C.</p> <p>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. Class IIa, Level of Evidence C</p> <p>Strategies to enhance maturity and independence may be particularly helpful in the adolescent HT recipients. Class IIa, Level of Evidence C</p> <p>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. Class IIa, Level of Evidence C.</p> <p><b>New Recommendations</b></p> <p>Each HT center should closely collaborate with a specialized nurse or liaison psychiatry who can screen and monitor 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.</p>	<p>Given its high prevalence and negative impact on graft function and survival both in pediatric and adult heart transplantation, adherence with the prescribed regimen should be routinely assessed at every HT outpatient clinic visit. <b>Class IIa, Level of evidence: B</b></p> <p>Electronic monitoring may be considered the gold standard for adherence assessment, as it allows capturing day-to-day variation in medication intake habits. However, electronic monitoring may not be feasible for all patients. Assessment methods should be combined to increase accuracy of adherence evaluation, e.g., by calculating the variability in trough values over time and using a validated self-report instrument (e.g., BAASIS). <b>Class IIa, Level of Evidence C</b></p> <p><b>Recommendation removed: combined with below</b></p> <p>Factors hindering adherence should be discussed in an open, non-threatening way during visits with HT recipients. Patient-related factors most consistently associated with medication nonadherence which require ongoing assessment and attention are knowledge and skill levels, intention and/or motivation, and potential barriers (defined as personal or environmental constraints preventing people from acting upon their intentions). <b>Class IIa, Level of Evidence C.</b></p> <p>Interventions should be discussed in close collaboration with the patient and his or her family and be tailored to the modifiable risk-factors. Strategies that seem most effective include offering education and skills training, reducing the complexity of the medication regimen, providing feedback on a patient's behavior, motivational interviewing, and combining strategies aiming to overcome barriers. Investment in long-term interventions is needed. <b>Class IIa, Level of Evidence: C.</b></p> <p>Continuing approval without change</p> <p>Continuing approval without change</p> <p>Attention should be given not only to adherence to the immunosuppressive regimen but also to adherence to other medications, as well as to all other health recommendations appropriate for HT recipients, because problems are prevalent and negatively impact post-transplant outcome. <b>Class IIa, Level of Evidence B.</b></p> <p>Continuing approval without change</p>

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*(Continued)***Topic 6: Psychologic Issues Particularly Related to Adherence to Medical Therapy and Management of Mood Disorders in Heart Transplant Recipients****2010 Prior Guideline Recommendation****2023 Guideline Update Recommendation**

Class IIa, Level of Evidence C.

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.

Class I, Level of Evidence C

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

Class I, Level of Evidence C

**New Recommendations****New Recommendations****New Recommendations**

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

Class I, Level of Evidence B.

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

Class I, Level of Evidence B.

Tricyclic antidepressants (e.g., imipramine, desipramine, amitriptyline, and clomipramine) are associated with cardiovascular toxicity (conduction delay, orthostatic hypotension, and anticholinergic effects) and may lower seizure thresholds, and therefore, their use should be restricted to HT recipients with severe

Given their impact on post-transplant survival, depressive symptoms should be regularly evaluated before and during long-term follow-up of HT recipients. This can best be done by user-friendly, validated screening instruments (e.g., PHQ-9, PHQ-9 modified for teens).

**Class I, Level of Evidence B**

All patients with elevated screening scores should be referred for specialized evaluation, assessment, and potential treatment. Each HT team should include a psychologist/psychiatrist who is qualified to detect and treat mood disorders. Patients with psychosocial problems or difficulty coping could be referred to appropriate mental and behavioral health services.

**Class I, Level of Evidence C**

Patients at risk should be monitored closely for presence of delirium immediately post-transplant by means of validated screening tools.

**Class I, Level of Evidence C**

Management for acute delirium should include treatment with antipsychotic medications, as per program protocol. Nonpharmaceutical interventions can include sleep protocols, mobilization, and cognition stimulation.

**Class I, Level of Evidence C**

Pediatric and adolescent HT patients are at greater risk of mental health comorbidities related to the psychological and physical changes associated with puberty. This may be further complicated by changing parent-child and peer relationships. Pediatric HT programs should have access to psychiatric services, with consideration to integrating child psychiatry into the pediatric transplant team.

Screening for depression and mood disorders should be routine practice, before, during and after transplantation with attention to the family unit and referral to a psychologist or social worker for routine follow up and support.

Pediatric HT programs should have specialized services in place to support the child and family through the transplant trajectory and transition to adult services.

**Class IIa, Level of Evidence C**

Continuing approval without change

Continuing approval without change

Tricyclic antidepressants (e.g., imipramine, desipramine, amitriptyline, and clomipramine) are associated with cardiovascular toxicity (conduction delay, orthostatic hypotension, and anticholinergic effects) and may lower seizure thresholds, and therefore, their use should be restricted to HT recipients with severe

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**Topic 6: Psychologic Issues Particularly Related to Adherence to Medical Therapy and Management of Mood Disorders in Heart Transplant Recipients**


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**2010 Prior Guideline Recommendation**

depression refractory to other therapies. Monoamine oxidase inhibitors (MAOIs) should be avoided because of their hypotensive effects, interactions with aesthetic 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.

Class I, Level of Evidence B.

**2023 Guideline Update Recommendation**

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.

**Class I, Level of Evidence B**

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**Topic 7: Substance use and abuse**

Tobacco, alcohol, and illicit substance use and abuse following heart transplant, increases the risk of non-adherence and allograft dysfunction and mortality.<sup>19, 26, 873</sup> Routine screening should be embedded in programs to support recipients/families, including evaluation by a multidisciplinary team that include social work, psychiatry, and/or psychology. With referral systems in place to addiction services for intervention as required.<sup>874, 875</sup> Patients with

previous tobacco or substance use before transplant are high risk for recurrence post, and a non-judgmental and supportive approach for screening is recommended.<sup>876, 877</sup> E-cigarettes as a cessation aid should be avoided due to limited evidence from randomized controlled trials. Vaping is also associated with cardiovascular and respiratory disease.<sup>878–881</sup> Patients should be counseled about the detrimental effects of tobacco, alcohol and illicit substance use, with emphasis on avoidance of cannabis regardless of legalization in some countries.<sup>882–884</sup>

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**Topic 7: Substance Use and Abuse**


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**2010 Prior Guideline Recommendation-None****2023 Guideline Update Recommendation***New Recommendations on Smoking***New recommendations**

Active tobacco use (smoking, chewing) is a risk factor for poor outcomes after transplantation and should be considered an absolute contraindication for transplantation.  
**Class IIa, Level of Evidence B**

**New recommendations**

Education on the importance of tobacco cessation and reduction in environment or second-hand exposure should be performed throughout the post-transplant period  
**Class I, Level of Evidence: C**

**New recommendations**

Patients with a smoking history (either pre- or post-transplant) should be regularly screened for smoking resumption, using reliable, objective measures.  
**Class IIb, Level of Evidence B**

**New recommendations**

All patients who resume tobacco smoking should be referred to an appropriate specialist for evaluation and possible cessation therapies that may include pharmaceutical and non-pharmaceutical aids.  
**Class IIb, Level of Evidence B**

**New recommendations**

E-cigarettes should be avoided as a tobacco cessation aid, as there is limited data to support either efficacy as a smoking cessation aid or safety of long-term use. Vaping is also associated with cardiovascular and respiratory disease.  
**Class III, Level of Evidence: C**

*Recommendations on Alcohol Use***New recommendations**

All patients should be routinely assessed and questioned on alcohol use.  
**Class I, level of Evidence C**

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*(Continued)***Topic 7: Substance Use and Abuse**2010 Prior Guideline  
Recommendation-None

2023 Guideline Update Recommendation

<b>New recommendations</b>	Patients that exceed national recommendations for “safe drinking” should be counselled on the harmful effects of alcohol. <b>Class I, Level of Evidence C</b>
<b>New recommendations</b>	If screening identifies misuse or dependency, then prompt referral to local specialty services for treatment and support is recommended. <b>Class I, Level of Evidence C</b>
	<i>Recommendations on Illicit Drug Use</i>
<b>New recommendations</b>	All patients should be routinely assessed and questioned regarding substance use (opioids, methamphetamine, and cocaine). <b>Class I, level of Evidence C</b>
<b>New recommendations</b>	Patients screened as at-risk for substance use should be tested for evidence of illicit substances. Positive testing for illicit substances requires prompt referral to local specialty services for treatment and support. <b>Class I, Level of Evidence C</b>
<b>New recommendations</b>	While cannabis or cannabinoids for medicinal purposes are commercially available in some areas, HT recipients should be advised to avoid these products, as recent findings suggest potentially dangerous interactions with immunosuppressive medications. Cannabis dependence is also associated with an elevated risk for nonadherence or other negative health behaviors, (e.g., alcohol use, medication taking), and might also negatively affect long-term graft function. <b>Class I, Level of Evidence C</b>

**Topic 8: Endocarditis prophylaxis after heart transplantation****Topic 8: Endocarditis Prophylaxis After Heart Transplantation**

2010 Prior Guideline Recommendation

2023 Guideline Update Recommendation

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 antibiotic prophylaxis for dental procedures is considered reasonable in patients with valvulopathies.  
Class IIa, Level of Evidence: C

Continuing approval without change.

**Topic 9: Return to work or school and occupational restrictions after heart transplantation**

Return to work is associated with a better health-related quality of life and lower physical and psychosocial disability in the short and longer term post-transplant.<sup>885–888</sup> Few HT recipients return to work despite feeling capable post-transplantation. Health care professionals, insurers, and employers should encourage and support return to work for HT recipients.<sup>889–892</sup> Adjusting the work schedule and duties should be considered for pre-transplant patients to

encourage remaining employed before transplantation and ease return to work after HT.<sup>889, 890, 892, 893</sup> Return to work goals should be discussed before transplantation and included within discharge planning after HT. When possible, employment should be resumed within the first 6 months post-transplant, as return to work becomes unlikely if delayed extensively.<sup>890, 892</sup>

Pediatric and adolescent heart transplant patients can return to school after initial recovery. Developmental outcomes span the range from normal to subnormal and may require targeted support for areas of deficit.<sup>893–895</sup> School-

aged transplant recipients should be formally screened for neurodevelopmental deficits after heart transplantation to better facilitate involvement of developmental specialists or

educational assistance if required.<sup>894, 895</sup> Special consideration should be given to the potential of infectious exposure in the school-aged population.

#### Topic 9: Return to Work or School and Occupational Restrictions After Heart Transplantation

##### 2010 Prior Guideline Recommendation

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

Class IIa, Level of Evidence: C.

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

Class IIa, Level of Evidence: C.

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

Class IIa, Level of Evidence: C.

##### **New recommendation**

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

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 postoperative rehabilitation.

Class IIa, Level of Evidence: C.

##### **New recommendation**

##### 2023 Guideline Update Recommendation

Health care providers, insurers, and employers should recognize that returning to work for HT recipients is possible and should provide support and encouragement for recipients to resume work.

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

Return to work should be the goal of post-transplant rehabilitation, and not an exception, given that post-transplant employment is associated with a better health-related quality of life and lower physical and psychosocial disability in the short and longer term post-transplant.

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

Patients should be encouraged to maintain their jobs as long as possible before HT as a shorter duration of unemployment before transplantation facilitates return to work after HT. A reduction in working hours or job content should be considered depending on the patient's physical condition.

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

Short-term and long-term goals for returning to work should be discussed before transplantation as well as part of the discharge planning after HT. Depending on the job content and post-transplant physical recovery of the patient, employment should be resumed within the first 6 months post-transplant, as return to work becomes unlikely afterwards.

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

Continuing approval without change.

##### **RETURN TO SCHOOL**

Transplant professionals should be aware that pediatric and adolescent heart transplant patients are able to return to school after initial recovery. Developmental outcomes span the range from normal to subnormal and these individuals may require targeted support for identified areas of deficit. Also, pediatric HT recipients may have specialized needs around infectious exposures that put them at serious risk (more so than their non-immunocompromised peers) and require consideration of placement in the classroom or accommodations to continue to learn

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Topic 9: Return to Work or School and Occupational Restrictions After Heart Transplantation

2010 Prior Guideline Recommendation

2023 Guideline Update Recommendation

**New recommendation**

while avoiding potentially dangerous infections.

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

School-aged transplant recipients should be formally screened for neurodevelopmental deficits after heart transplantation and educational assistance should be provided in case of learning disabilities. Referral to developmental specialists should be considered.

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

**Topic 10: Return to operating a vehicle after heart transplantation**

The 2010 recommendations for the operation of a vehicle after heart transplantation (HT) were reviewed, and the details of the former and updated versions are summarized in the recommendations below. The decision regarding whether a HT recipient can resume driving should consider the balance between minimizing driving-related road safety risks for the individual and the community posed by the driver’s permanent or long-term injury or disability while also understanding the driver’s lifestyle and employment-related mobility independence.<sup>896, 897</sup> The updated recommendations highlight the heterogeneity of this group of patients.<sup>898–901</sup> Hence, the assessment of a patient’s ability to drive a motor vehicle should be undertaken on a case-by-case basis, taking into consideration specific clinical and functional issues and in compliance with any change in the status of each case.<sup>898–901</sup> Recommendations in the current document distinguish between drivers of private vehicles

(group 1) and professional drivers (group 2) while addressing the specific requirements for each group.<sup>898–901</sup>

Regardless of the group, attention must be given to those drivers considered to be higher risk drivers, such as drivers of taxis and ambulances and other professional drivers who spend many hours per day behind the wheel or who transport passengers most of the time. With regard to the timing of resuming driving, a "non-driving" period of 6 weeks and 3 months for groups 1 and 2, respectively, is reasonable for patients with an uneventful recovery.<sup>896, 898, 899, 902</sup>

Appropriate recommendations have been added for significant problems that can occur, for example, arrhythmias, malignant hypertension, diabetes mellitus, heart failure, rejections and cardiac allograft vasculopathy.<sup>645, 648, 896–898, 900–906</sup>

Higher risk drivers should be reviewed with a high level of scrutiny. Immunosuppressant nonadherence is linked to poor outcomes and entails serious risks, and it should thus be carefully considered when a return to operating a vehicle after heart transplantation is assessed.<sup>844</sup>

Topic 10: Return to Operating a Vehicle After Heart Transplantation

2010 Prior Guideline Recommendation

2023 Guideline Update Recommendation

Assessment and discussion of the ability to drive a motor vehicle should be included in the early follow-up of HT recipients. Class I, Level of Evidence: C.

Assessment and discussion of the ability to drive a motor vehicle should be included in the early follow-up of HT recipients, and after any change in clinical and functional status.

**Class I, Level of Evidence: C.**

**New recommendation**

The population of HT recipients is heterogeneous. Hence, individual assessment of the ability to drive a motor vehicle should be undertaken with consideration of the following clinical and functional issues:

- Neurologic abnormalities
- Diabetes mellitus
- Hypertension
- Cardiac allograft vasculopathy
- Treated rejection episodes
- Heart failure
- Arrhythmia

The medical assessment should be conducted by a health professional which may be the patient’s general practitioner. Certain

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## Topic 10: Return to Operating a Vehicle After Heart Transplantation

## 2010 Prior Guideline Recommendation

## 2023 Guideline Update Recommendation

**New recommendation**

medical conditions may require evaluation by a specialist to obtain clearance for operating a motor vehicle. Depending on locale, physicians may be required to report the presence of certain medical conditions that interfere with driving to the appropriate authority or agency.

**Class I, Level of Evidence: B**

Drivers should be divided into two groups:

Group 1 drivers of private vehicles: small and low-weight vehicles (i.e., motorcycles, passenger cars and other small vehicles with or without a trailer)

Group 2 professional drivers: Large and high-weight vehicles, typically for professional and commercial use (i.e., vehicles over 3.5 tons or vehicles designed for transporting more than nine passengers, including the driver).

**Class I, Level of evidence: B****New recommendation**

Timing of driving after HT: Driving may be allowed after sufficient wound healing, clinical recovery, and return to normal physical and cognitive functioning.

**Class I, Level of evidence: B****New recommendation**

Group 1: Driving may be allowed if the recipient is clinically stable (with reference to: neurologic abnormalities, diabetes mellitus, malignant hypertension, CAV, treated rejection episode, heart failure, and arrhythmia).

Group 2: Driving may only be allowed after intentional individual assessment by a specialist.

**Class I, Level of evidence: B**

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

Class I, Level of Evidence: C.

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

Class I, Level of Evidence: C.

Continuing approval without change.

Arrhythmias should be considered separately: bradycardia, branch blocks, supraventricular tachycardias, ventricular arrhythmias, long QT syndrome, and Brugada syndrome. A history of syncope and the presence of limiting symptoms must be considered before driving is permitted, as well as each treatment.

**Class I, Level of Evidence: C.**

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

Class I, Level of Evidence: C.

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

In patients with known diabetes mellitus, unpredictable hypoglycemia may impair ability to drive and should also be assessed.

**Class I, Level of Evidence: C.****New recommendation**

Absence of malignant hypertension should be ascertained before HT recipients are permitted to drive.

**Class I, Level of Evidence: C.****New recommendation**

Assessment of the New York Heart Association classification of heart failure (NYHA) functional class. For NYHA<IV driving is permitted for group 1, and NYHA<III for group 2.

**Class I, Level of Evidence: C.****New recommendation**

CAV: individual clinical assessment is recommended with reference to graft dysfunction, CAV severity and history of treated

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## Topic 10: Return to Operating a Vehicle After Heart Transplantation

## 2010 Prior Guideline Recommendation

**New recommendation**

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

Class I, Level of Evidence: C.

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.

Class I, Level of Evidence: C.

## 2023 Guideline Update Recommendation

rejection within 2 years of CAV diagnosis.

**Class I, Level of Evidence: B.**

Following a hemodynamically significant allograft rejection episode, the HT recipient should refrain from driving for 2 weeks after the episode

**Class I, Level of Evidence: B.**

Continuing approval without change.

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

**Class I, Level of Evidence: C.**

**Topic 11: Family screening****Part 1. Pathological diagnosis of the explanted heart**

*Accuracy of pretransplant diagnoses.* Although efforts are made to identify the etiological cause for heart failure before transplantation, even when a pre-transplant diagnosis is assigned, discrepancies exist when subsequent pathological studies are performed.<sup>907–910</sup> Although other diagnoses such as myocarditis and iron-overload cardiomyopathy<sup>909, 911</sup> are elucidated in the pathological analysis of the explanted heart, cardiac sarcoidosis, and genetic diseases seems to be the most commonly unrecognized diagnoses.<sup>908, 910</sup>

*Implications of explanted heart diagnosis correct diagnosis.* Recognizing that diagnoses such as cardiac sarcoidosis and genetic cardiomyopathies may not represent a large segment of the transplanted population, correct diagnoses may affect

allocation, pre- and post-transplant care/surveillance, as well as have significant family counseling implications.<sup>910</sup> Additionally, analysis of the explanted heart can help clinicians better understand the pathophysiology of disease<sup>912–919</sup> as well as evaluate the utility of cardiac investigations in the management of end-stage heart failure population, spurring advances in clinical care, and research endeavors.<sup>920–923</sup> Furthermore, in an era when an increasing number of patients are being bridged to transplant with ventricular assist therapy, explanted heart studies can help us understand the effects of this therapy on the native heart.<sup>924</sup>

Similar benefits would be expected from the pathological analysis of explanted allografts and in the pediatric population.<sup>921, 925–928</sup>

**Sample procedures for explanted heart analysis**

A systematic and thorough examination of the explanted heart should be performed (Table 15).

## Topic 11: Family Screening

## Part 1. Pathological Diagnosis of the explanted heart

## 2010 Prior Guideline Recommendation-None

**New Recommendation**

## 2023 Guideline Update Recommendation

Pathological examination of the explanted native heart is recommended for all transplants.

**Class I, Level of Evidence B**

Pathological examination of the explanted allograft heart is recommended for all re-transplants.

**Class I, Level of Evidence C**

Examination of the explanted organ should include gross, histological, and appropriate genetic testing (Table 15)

**Class I, Level of Evidence C**

Outcomes of the explanted heart examination should be conveyed to the primary heart transplant team, so they can inform the patient and discuss management decisions, including family counseling as appropriate.

**Class I, Level of Evidence C**

**Table 15** Sample Procedures for Pathological Examination of the Explanted Hearts

- 1) Appropriated photographic documentation of the intact and the sectioned hearts should be performed.<sup>929</sup>
- 2) Preferably before fixation in 10% formalin, sampling of fresh myocardium from the four cavities taking multiple small fragments to be frozen for genetic and molecular analysis, and to be fixed in Karnovsky/glutaraldehyde for electron microscopy for diagnostic and for research purposes.
- 3) Gross examination before sectioning according to standard protocols, which take into consideration the different types of pathologies, which have led to transplant.
- 4) Sectioning according to the different types of pathologies:
  - for cardiomyopathies, ischemic heart disease, and valve diseases transverse cut from apex to the base of the heart.
  - for congenital heart disease the transverse cut is not recommended but use the sequential segmental approach
- 5) Histological sampling of the entire circumferential midventricular transverse cut and of the coronary arteries for multiple appropriate staining including immunohistochemistry
- 6) In case of mechanical assistance device implantation before transplant it would be important to evaluate grossly the device before removing it. In case of interventional procedures, both percutaneous and surgical, on the coronary arteries and on the valves particular care should be adopted for stents, valve, and vascular prosthesis with specific technique.

**Topic 11: Part 2. Family screening**

Counselling of heart transplant recipient will need to consider the ethology of HF before transplant, severity of the disease, extent, and implications of all associated abnormalities. This can be challenged by the wide spectrum of the underlying anatomy, the lack of risk predictors and validated biomarkers for disease progression and the paucity of evidence demonstrating treatment efficacy. Appropriate counselling will allow patients and their relatives to consider various options and be prepared for subsequent treatments.<sup>930, 175</sup>

Genetic testing is recommended to confirm diagnosis or formulate a differential diagnosis among overlapping

phenotypes. The goals of genetic counselling are to increase patient’s knowledge and awareness of their disease and its genetic aspect, explain importance of genetic information for their kindred and help in risk stratification.<sup>931</sup>

Patients with a family history of malignancies whether they have had a malignancy or not pre-transplant should undergo genetic screening. The genes to be checked will depend on the malignancy. Family member screening should be guided by family and genetic histories. Individual discussion and consideration could be given as to whether prophylactic surgeries (i.e., mastectomies, oophorectomies) should be performed in patients with strong family histories from breast or ovarian cancer.<sup>932, 933</sup>

Topic 11: PART 2 - Family Screening  
Counseling on Heart Failure (HF) Etiology

2010 Prior Guideline  
Recommendation-None

2023 Guideline Update Recommendation

**New recommendation**

Providers should have a thorough knowledge of an individual transplant recipient’s previous anatomy and physiology including review of all surgical and procedural records. In case of CHD background, a fetal ECHO is warranted in the offspring. The parents should be counseled by a pediatric cardiologist specialized in fetal cardiology in close co-operation with the fetal medicine specialist team. The working relationship between multidisciplinary team members is essential for patient management to improve outcome.

**Class I, Level of Evidence: C**

**New recommendation**

Genetic testing is recommended in all patients with suspected genetic abnormality, and history of parental consanguinity, preferably during evaluation for heart transplantation, alternatively in patients who have had a heart transplant.

Once a causative mutation is found in the proband, genetic testing of first-degree family member is indicated.

**Class I, Level of Evidence: C**

**New recommendation**

Patients with a family history of malignancies whether they have had a malignancy or not pre-transplant should undergo genetic screening. The genes to be checked will depend on the malignancy.

- Specifically, patients with a history of breast or ovarian cancer should be checked for the BRCA-1 and BRCA-2 genes. Consideration should be given as to whether prophylactic surgeries (i.e., mastectomies, oophorectomies) should be performed in patients with strong family histories from breast, ovarian cancer who are BRCA-1+ or BRCA-2+.

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Topic 11: PART 2 - Family Screening  
Counseling on Heart Failure (HF) Etiology

2010 Prior Guideline  
Recommendation-None

2023 Guideline Update Recommendation

- There are other genes which predispose to malignancies. For example, CDH1 predisposes to the development of gastric carcinoma and these patients, regardless of whether they undergo transplant, should undergo prophylactic gastrectomy. This strategy should be considered in patients who have this genetic abnormality and who are being evaluated for heart transplantation or have had a heart transplant.
- Patients with known gene mutations, family histories of malignancies and either with prior malignancies or who do not have these should be referred to Cancer Risk and Assessment Programs at Cancer Centers.
- Post-transplant screening should be determined by the genetic risk and may be different and more stringent than what is recommended by the American Cancer Society and the U.S. Preventive Services Task Force.

**Class I, Level of Evidence: C**

## Topic 12: A management of the transition from pediatric to adult care after heart transplantation

Transition from pediatric care to adult care after HT requires significant advanced preparation of the multidisciplinary team, the patient's family and most importantly the HT recipient. Understanding and awareness of short and long-term effects of chronic immunosuppression and life-long medical care are essential.<sup>934</sup> Discussions surrounding reproductive health and sexuality are necessary aspects to medical care for pregnancy prevention and minimizing risks of STI.<sup>935</sup> To aid transition, health care team members should begin the process by involving the patient in medical

decision making.<sup>428, 936</sup> Education which involves a structured transition plan should begin at age 12 and follow the patient through to early adulthood. Educational "transition of care" tool kits are available and may aid the transition process.<sup>937</sup> Technological applications that assist with medication and appointment reminders are often preferred by younger patients and can help prevent non-adherence. Developing a clinic or waiting room option for pediatric patients transitioning to adult care has been well received. A clinic option for patients from 12 years old to early adulthood has been shown to increase overall patient satisfaction and should be considered when feasible.<sup>938–941</sup>

Topic 12: A Management of the Transition from Pediatric to Adult Care After Heart Transplantation

2010 Prior Guideline Recommendation

2023 Guideline Update Recommendation

Critical milestones to be achieved by pediatric HT recipients before transition to adult care include:

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), along with repetition is necessary to ensure understanding of the clinical condition by the HT recipient.

Awareness of the long- and short-term clinical implications of chronic immunosuppression (infection prevention, cancer surveillance, academic, and vocational aspirations).

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).

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

Continuing approval without change.

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## Topic 12: A Management of the Transition from Pediatric to Adult Care After Heart Transplantation

## 2010 Prior Guideline Recommendation

## 2023 Guideline Update Recommendation

of symptoms and signs requiring immediate medical attention and understanding of health care coverage and eligibility requirements).

Class I, Level of Evidence: C.

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

Class I, Level of Evidence: C.

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.

Class I, Level of Evidence: C.

**New recommendation**

Continuing approval without change.

Continuing approval without change.

Pediatric transplant care providers should prepare the patient for transition from pediatric care to adult care by encouraging a move toward independence demonstrated by taking on self-care responsibilities and involvement in decision-making.

**Class I, Level of Evidence: C**

**New recommendation**

Structured transition program for adolescent heart transplant recipients should be adopted by pediatric heart transplant centers to increase knowledge and decrease non-adherence.

**Class I, Level of Evidence: C**

**New recommendation**

A transition education preparation should begin from age 12 and continue into the early twenties.

**Class I, Level of Evidence: C**

**New recommendation**

The following resources should be considered and used to aid in care transitions. Evolving development of these resources may lead to limited availability in some areas.

- Tailored solutions to help adolescents take their medications should be explored. Technology such as smart phones can help prepare adolescents through apps, for example setting alarms to avoid forgetfulness, but given that nonadherence is a multi-faceted problem, several options should be considered taking the adolescent's preferences into account.
- The American College of Cardiology has produced a transition of care tool kit, which can be adapted to the practice patterns of international transplant centers. This includes a transition readiness self-assessment (which allows health care providers to assess an adolescent's likelihood for successful transition), knowledge assessments, clinical summaries, and emergency care plans that young people can keep and share with adult providers.
- Health care providers should consider developing clinic times or waiting room options more inviting for pediatric patients transitioning to adult care. A clinic option for patients from 12 years old to early adulthood has been shown to increase overall patient satisfaction and should be considered when feasible.

**Class I, Level of Evidence: C**



Topic 13: Principles of Shared Care After Heart Transplantation	
2010 Prior Guideline Recommendation	2023 Guideline Update Recommendation
<p>The HT team should ensure that other involved physicians always know telephone numbers and electronic mail addresses of the HT team to enable contact and guarantee prompt responses to referring physician queries. Class I, Level of Evidence: C.</p> <p>It is helpful for physicians outside the HT team to receive the patient's plan for scheduled HT office visits at the transplant center. Class I, Level of Evidence: C.</p> <p>Formal procedures should be instituted to regularly inform the referring physician of clinical results and medical regimens. Class I, Level of Evidence: C.</p> <p><b>New recommendation</b></p>	<p>The HT team should ensure that other involved physicians are provided telephone numbers and electronic mail addresses of the HT team to enable contact and guarantee prompt responses to local physician queries. Primary care physicians should be encouraged to follow the patient along with the HT team to allow shared care as the patient gets further away from transplant surgery. Continuing approval without change.</p> <p>Continuing approval without change.</p> <p>Once stable, the care of patients is increasingly shared with local physicians. The transplant center should ensure the local center/physician has sufficient expertise in post-transplant management. Ensuring adequate exchange of center specific protocols for post-transplant would allow for a seamless transition of care. <b>Class I, Level of Evidence: C</b></p> <p>The HT team should have periodic conference calls with the local centers to discuss the care of these patients, to enable ongoing discussions and review appropriate management of complications, should they arise. These might include medical complications, but also psychological, social, or health behavior problems. <b>Class I, Level of Evidence: C</b></p>
<p><b>New recommendation</b></p>	

### Topic 13: Principles of shared care after heart transplantation

The care of HT recipients involves a multi-disciplinary team and often includes several providers or specialists. Timely communication with referring physicians, specialists, and primary care providers is necessary to ensure plan of care implementation and prevent complications. The HT team should have an identified process for relaying patient clinical information. The HT team should encourage the primary care physician to share in the care of the HT recipient by clear communication of protocols and patient health information. The patient and primary care physician should know how to reach the transplant center in case of emergency.

### Topic 14: Traveling after heart transplantation

Potential travel should be discussed with heart transplant recipients and referral to travel medicine with expertise in immunocompromised hosts is recommended to receive information about safer travel including but not limited to

food and water safety, zoonotic infections, arthropod-borne infection, sexually transmitted infections, and malaria prophylaxis.<sup>942, 943</sup>

Travel to high-risk destinations is not recommended in the first-year post-transplant.<sup>944</sup> Travel out of country to low-risk areas may be allowable for patients 3 to 6 months post-transplant who are doing well given the planned destination has access to medical care. Patients should take enough medications for travel duration and keep medications in nearby hand luggage while in flight.<sup>943–945</sup>

- Vaccination:<sup>52, 943</sup> Routine vaccinations should be up to date. Travel-specific vaccinations will depend on the planned destination.<sup>52, 147, 945, 946</sup> Live-vaccines should NOT be given to heart transplant recipients for travel (live attenuated influenza vaccine (LAIV), oral typhoid, oral polio, varicella or live zoster vaccine, MMR, BCG, or Yellow Fever; live-attenuated Japanese Encephalitis (JE) Virus vaccine not recommended, but inactivated JE vaccine is recommended).

## Topic 14: Traveling After Heart Transplantation

2010 Prior Guideline Recommendation-None	2023 Guideline Update Recommendation
<b>New recommendation</b>	Potential travel should be discussed with heart transplant recipients and referral to travel medicine with expertise in immunocompromised hosts is recommended to receive information about safer travel including but not limited to food and water safety, zoonotic infections, arthropod-borne infections, and sexually transmitted infections, and malaria prophylaxis. <b>Class I, Level of Evidence: C.</b>
<b>New recommendation</b>	Travel to high-risk destinations is not recommended in the first-year post-transplant. <b>Class I, Level of Evidence: C</b>
<b>New recommendation</b>	Routine non-live viral vaccinations should be up to date. <b>Class I Level of Evidence: A (unrelated to travel)</b> <b>Class I, Level of Evidence C (related to travel)</b>
<b>New recommendation</b>	Travel-specific vaccinations will depend on the planned destination. <b>Class I, Level of Evidence: C</b>
<b>New recommendation</b>	Live-viral vaccinations should NOT be given to heart transplant recipients for travel (Live attenuated influenza vaccine (LAIV), oral typhoid, oral polio, varicella or live zoster vaccine, MMR, BCG, or Yellow Fever; live-attenuated Japanese Encephalitis (JE) Virus vaccine not recommended, but inactivated JE vaccine is recommended). <b>Class III, Level of Evidence: C</b>

## Topic 15: Emerging pathogens, epidemics, and pandemic considerations for heart transplant recipients-new topic

### *Heart transplantation during pandemics, emerging pathogens, and public health emergencies*

The 2009 influenza A/H1N1 and 2019 coronavirus disease (COVID-19) pandemics have posed challenges to healthcare systems internationally and have had significant ramifications for organ transplantation. These pandemics, in addition to the 2002 Severe Acute Respiratory Syndrome (SARS) and 2012 Middle East Respiratory Syndrome (MERS) epidemics, have highlighted the risk of respiratory viral disease transmission and underscored the importance of multidisciplinary approaches to transplantation, donor and recipient evaluation and management, and disease prevention in the setting of public health emergencies. Specific ISHLT recommendations regarding H1N1 influenza and cardiothoracic transplantation have been published previously,<sup>947</sup> and ISHLT guidance related to COVID-19 is being updated regularly at the time of this publication.<sup>948</sup> Herein, we provide general recommendations regarding heart transplantation during emergence of future novel pathogens, epidemics, and pandemics. This guidance is based upon previous experience with the previously mentioned viruses but is broadly applicable to future outbreaks involving pathogens with other mechanisms of transmission.

### *Ethical considerations*

Pandemics or the emergence of a novel pathogen poses significant demand on health care facilities and directly impact intensive care unit capacity, staffing, and capabilities for transitional and longitudinal outpatient care.<sup>949, 950</sup> Additional implications of organ transplantation in this context include the potential risk of donor-derived infection, disease transmission from donors to the transplant team, and nosocomial transmissions to health care workers and other hospitalized patients, as well as post-transplant infection acquisition.<sup>949, 951</sup> While temporary suspensions in transplant activity occurred during the SARS outbreak and beginning of the COVID-19 pandemic,<sup>952–954</sup> decisions regarding heart transplant activity during a pandemic should be made at the center level. It is important to keep in mind that heart transplant is lifesaving and deferral of transplant must be weighed against the risk of dying on the waitlist. Prepandemic contingency procedures and plans should be developed that help guide ongoing transplant activity during a pandemic based on local resource availability and organ allocation, presence of local community transmission, and risk of infectious complications while being guided by the principles of utility, justice, and efficiency.<sup>950</sup> In addition, all transplant candidates must be informed of the center's policy to address the risk of pandemic illness transmission<sup>947</sup> particularly as donor testing platforms and associated performance characteristics evolve.

## ***Dynamic multidisciplinary approach to evaluation and management***

During emergence of novel pathogens, evolving epidemiology and lack of evidence-based guidance pose significant challenges to the evaluation and management of donors and heart transplant recipients. Therefore, a multidisciplinary approach involving transplant infectious diseases is imperative when considering issues including but not limited to: assessment of disease risk in donors and potential recipients at the time of organ offer, procurement procedures and other issues germane to infection control, and management of heart transplant recipients with active infection, including the use of investigational therapeutics, alterations in immunosuppressive therapy, and timing of biopsies and other invasive procedures.

Management strategies must be continually updated by evolving scientific literature and public health guidance.

### ***Disease prevention***

Communication with patients and caregivers is key for effective infection prevention practices. This includes education regarding the infection, methods of transmission, hand hygiene, masks for respiratory illness, and social distancing as necessitated by the mode of transmission of the emerging pathogen or pandemic illness.<sup>947, 951</sup> Strategies to minimize potential healthcare exposures are dependent upon disease transmission dynamics; however, centers should consider deferral of routine outpatient visits and procedures for stable patients, particularly in the setting of a novel respiratory pathogen. Extensive use of telemedicine during the COVID-19 pandemic demonstrates that this is an effective strategy for ongoing outpatient management. In order to further mitigate disease transmission, previous epidemics and pandemics have also underscored the need to screen patients and visitors for illness upon arrival to health care facilities and to develop processes by which transplant recipients can be rapidly and safely evaluated should they become ill.<sup>951</sup> Finally, issues surrounding the timing of vaccination and role of chemoprophylaxis should be addressed by the heart transplant team and transplant infectious diseases as applicable. Whenever possible, efforts should be made to reduce visits by clinically stable heart transplant patients to medical facilities by shifting blood testing to the patients' homes. Consideration should be given to remote drawing of blood samples which include gene expression profiling and donor derived cell-free DNA assays. This home-based testing can potentially reduce the need for surveillance endomyocardial biopsy and thereby limit hospital visits. Such options should be considered when applicable.

### ***Patient management during a pandemic***

Considerations for management of heart transplant patients during a pandemic are influenced by the COVID-19 health-care crisis. General principles in managing heart transplant

patients during this pandemic may be applicable to future epidemics or pandemics. These approaches are guided by recommendations from governmental health-care agencies such as the Centers for Disease Control (CDC) in the United States and professional societies such as the ISHLT. In both circumstances, recommendations are often updated based on new information. During the COVID-19 pandemic, recommendations were delineated in the ISHLT Guidance for Cardiothoracic Transplant and VAD Centers.<sup>948</sup> These recommendations should be reviewed and followed. As previously mentioned, efforts should be made to reduce visits by clinically stable heart transplant patients to medical facilities by shifting blood testing to the patients' homes when applicable. Regarding vaccination against COVID-19, the following considerations recommended by the ISHLT and other transplant organizations include:

- 1 Pretransplant vaccination of all SOT candidates as a priority whenever feasible.
- 2 Continued SARS-CoV-2 vaccination in SOT recipients and priority for vaccination of their household members and caregivers to reduce exposure risk for these vulnerable patients.
- 3 Continuation of a stable immunosuppression regimen at the time of vaccination to avoid the risk of organ rejection until more comprehensive data are available.
- 4 Continued adherence of all transplant recipients to protective measures including masking and social distancing regardless of vaccination status.

Studies have demonstrated that antibody response to the COVID-19 vaccines are not as robust in transplant recipients as in non-transplant patients.<sup>953</sup> A randomized clinical trial of a third dose of the mRNA-1273 vaccine (Moderna) versus placebo in transplant recipients who had already received two doses showed enhanced immune response against Covid-19.<sup>955</sup> These studies support a COVID-19 booster or third injection of mRNA vaccine enhances the antibody response and this approach is now recommended by governmental health-care agencies. Reduced efficacy of new vaccines in the transplant recipient should be considered during a pandemic crisis and proper education given on minimizing exposure risks. Ongoing updates and recommendations during a pandemic response will be made through transplant societies such as ISHLT as well as governmental health agencies. These updates will be available on websites as additional clinical studies and information become available. The ISHLT recommendations include the following statement: "Based on current evidence, we recommend providing a third dose of mRNA vaccine for SOT recipients that have previously completed a 2-dose mRNA vaccine series if local regulations allow; The use of a third dose should, until further evidence is available, be based on individual patients' unique situation and must depend on local availability of vaccines and local regulations."<sup>948</sup>

## TOPIC 15: Emerging Pathogens, Epidemics, and Pandemic Considerations for Heart Transplant Recipients

2010 Prior Guideline  
Recommendation-NONE

2023 Update Guideline Recommendation

**New recommendation*****Ethical Considerations***

Temporary suspensions in transplant activity may occur during a pandemic. Decisions regarding heart transplant activity should be made at the transplant center level. As heart transplantation is lifesaving, deferral of transplant must be weighed against the risk of a patient dying on the wait-list.

Pre-pandemic contingency procedures and plans should be developed that help guide ongoing transplant activity during a pandemic based on local resource availability and organ allocation, presence of local community transmission, and risk of infectious complications while being guided by the principles of utility, justice, and efficiency.

Transplant candidates must be informed of the center's policy to address the risk of novel pathogen and pandemic illness transmission, particularly as donor testing platforms and associated performance characteristics evolve.

**Class I, Level of Evidence: C****New recommendation*****Dynamic Multidisciplinary Approach to Evaluation and Management***

A multidisciplinary approach involving transplant infectious diseases is imperative when considering issues including but not limited to:

assessment of disease risk in donors and potential recipients at the time of organ offer,

procurement procedures and other issues germane to infection control,

management of heart transplant recipients with active infection, including the use of investigational therapeutics,

alterations in immunosuppressive therapy, and timing of biopsies and other invasive procedures.

Management strategies must be continually updated by evolving scientific literature and public health guidance.

**Class I, Level of Evidence: C****New recommendation*****Disease Prevention***

Patient and caregiver education regarding the novel pathogen or pandemic infection, methods of transmission, hand hygiene, masks for respiratory illness, and social distancing as necessitated by the mode of transmission of the emerging illness is essential.

Centers should consider deferral of routine outpatient visits and procedures for stable patients, particularly in the setting of an emerging respiratory virus.

Extensive use of telemedicine demonstrates that this is an effective strategy for ongoing outpatient management during the emergence of a novel pathogen.

Patients and visitors should be screened for illness upon arrival to healthcare facilities and to processes should be developed by which transplant recipients can be rapidly and safely evaluated should they become ill.

Issues surrounding the timing of vaccination and role of chemoprophylaxis should be addressed by the heart transplant team and transplant infectious diseases as applicable.

**Class I, Level of Evidence: C*****Patient Management During a Pandemic***

Efforts should be made to reduce visits by clinically stable heart transplant patients to medical facilities by shifting blood testing to the patients' homes.

Remote drawing of blood samples can include screening tests to determine if patients require endomyocardial biopsies using gene expression profiling and donor derived cell-free DNA assays.

**Class I, Level of Evidence C*****Vaccination Against COVID-19***

The current ISHLT recommendations should be followed:

Pre-transplant vaccination of all SOT candidates as a priority whenever feasible.

Vaccination in SOT recipients and priority for vaccination of their household members and caregivers to reduce exposure risk for these vulnerable patients.

Continuation of a stable immunosuppression regimen at the time of vaccination to avoid the risk of organ rejection until more comprehensive data are available.

Live viral vaccines even if attenuated should be avoided. Use of vaccines with mRNA technology is safe in immunocompromised patients but efficacy may be reduced.

**Class I, Level of Evidence: C**

Data indicates reduced vaccine efficacy in immunocompromised patients. Serum antibody assessments to vaccination should be considered and potentially studied during emerging pathogens.

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*(Continued)*

## TOPIC 15: Emerging Pathogens, Epidemics, and Pandemic Considerations for Heart Transplant Recipients

2010 Prior Guideline

Recommendation-NONE

2023 Update Guideline Recommendation

**Class I, Level of Evidence C**

Reduced efficacy of new vaccines in the immunocompromised transplant recipient should be considered during a pandemic crisis and proper education given on need to minimize exposure risks despite vaccination.

**Class I, Level of Evidence C**

Based on current evidence, providing a third dose of mRNA vaccine for SOT recipients that have previously completed a 2-dose mRNA vaccine series is recommended. The use of repeated booster vaccines should be supported as further evidence is available. Ongoing booster vaccination should be based on the individual patient's unique situation and may depend on local availability of vaccines and local regulations.

**Class I, Level of Evidence B**

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