CARDIAC TRANSPLANTATION

Prepared by **Dr. Sidhartha Mullapudi**, DrNB (Cardiology), MD (General Medicine)
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I INDICATIONS FOR ORTHOTOPIC HEART TRANSPLANTATION (ISHLT 2016/2024 & ESC 2021 CLASS I)

- **End-Stage Heart Failure (Stage D):** Advanced systolic, restrictive, hypertrophic, or congenital heart failure with severe refractory symptoms (**NYHA Functional Class IIIb to IV** or **INTERMACS Profiles 1 to 4**), recurrent HF hospitalizations, or inotrope/mechanical circulatory support dependency despite optimal Quadruple GDMT, CRT, and structural interventions.
- **Cardiopulmonary Exercise Testing (CPET — Objective Gold Standard):**
  - **Patients on Beta-Blockers: Peak VO2 of 12 mL/kg/min or less** (with maximal effort confirmed by **Respiratory Exchange Ratio [RER] greater than 1.05**).
  - **Patients Intolerant of Beta-Blockers: Peak VO2 of 14 mL/kg/min or less**.
  - **Young Patients (<50 Years) and Women: Peak VO2 less than 50 percent of predicted**.
  - **Obese Patients (BMI >=30 kg/m2) or Submaximal Effort (RER <1.05): VE/VCO2 Ventilatory Efficiency Slope greater than 35** (or lean-body-mass-adjusted Peak VO2 <=19 mL/kg/min).
  - **Validated Survival Scores: Heart Failure Survival Score (HFSS)** in the high/medium-risk range or **Seattle Heart Failure Model (SHFM)** predicted 1-year survival **less than 80 percent**.
  - **Refractory Ventricular Arrhythmias or Angina:** Incessant, life-threatening **ventricular arrhythmias (electrical storm)** refractory to antiarrhythmic drugs, catheter ablation, and stellate ganglion block, or refractory severe angina not amenable to percutaneous or surgical revascularization.

II RECIPIENT EVALUATION AND CONTRAINDICATIONS (ISHLT GUIDELINES)

- **Fixed Pulmonary Hypertension (The Crucial Hemodynamic Contraindication):**
  - **Mechanism:** The thin-walled donor right ventricle is conditioned to a normal low-resistance pulmonary bed and will suffer **acute fatal Right Ventricular Failure** in the operating room if anastomosed against fixed high Pulmonary Vascular Resistance (PVR).
  - **Hemodynamic Cut-offs (ISHLT 2016):** A **Pulmonary Artery Systolic Pressure (PASP) of 50 mmHg or more** with either a **Transpulmonary Gradient (TPG = mPAP minus PCWP) of 15 mmHg or more** or a **PVR above 3 Wood Units** mandates an **acute vasodilator challenge**; a PVR that stays **above 5 Wood Units (or Indexed PVR above 6 Wood Units·m2)** markedly raises the risk of donor RV failure (using IV Sodium Nitroprusside, Inhaled Nitric Oxide, or Milrinone).
  - **Unloading Trial Before Listing:** If PVR fails to fall **below 3 to 5 Wood Units** acutely (or drops only at the expense of systemic hypotension, SBP <85 mmHg), a **24-to-72-hour ICU trial of continuous inotropes/vasodilators/IABP** or **durable Left Ventricular Assist Device (LVAD) implantation for 3 to 6 months** is performed to mechanically unload the left atrium and remodel the pulmonary vasculature; **if PVR remains irreversibly fixed above 5 Wood Units despite LVAD unloading, isolated orthotopic heart transplantation is contraindicated** (requiring heart-lung transplantation).
  - **Other Relative and Absolute Contraindications:**
  - **Age and Obesity:** Age >70 years (selected patients >70 yr may be considered via alternate-list criteria) and **Class II Obesity (BMI >=35 kg/m2)** (associated with poor post-transplant survival; weight loss to BMI <35 kg/m2 is recommended prior to listing).
  - **Active Malignancy or Infection:** Active neoplasm (other than non-melanoma skin cancer; requires oncology collaboration to define a low-recurrence remission window) or uncontrolled systemic infection.
  - **Irreversible Extracardiac Organ Dysfunction: Irreversible renal dysfunction (eGFR <30 mL/min/1.73 m2)** or **cirrhosis** is a contraindication to *isolated* heart transplantation, and requires **Simultaneous Heart-Kidney or Heart-Liver Transplantation**.
  - **Severe Peripheral/Cerebrovascular Disease, Diabetes with Severe End-Organ Damage, Active Substance/Tobacco Use within 6 Months, or Psychosocial Non-Adherence**.

III DONOR MATCHING, ALLOCATION AND ORGAN PRESERVATION

- **ABO Blood Group Compatibility:** Mandatory **ABO compatibility** (identical or compatible blood group) in adults. (**Pediatric Exception: ABO-incompatible heart transplantation** is safely performed in **infants under 1 to 2 years of age** before isohemagglutinin antibody production matures.)
- **Predicted Heart Mass (PHM) and Weight Sizing:** Donor-to-recipient **body weight ratio (0.8 to 1.2; or Predicted Heart Mass [PHM] within 20 to 30 percent)** is required; **undersizing a female donor heart into a larger male recipient by >20 to 30% PHM** is strictly avoided, especially if recipient PVR is mildly elevated.
- **Immunological HLA / PRA Screening:** Panel Reactive Antibody (**calculated PRA [cPRA]**) and single-antigen bead (Luminex) screening identify preformed **Donor-Specific Antibodies (DSA)**; a **Virtual Crossmatch** (or prospective cytotoxic/flow crossmatch plus perioperative desensitization with plasmapheresis/IVIG/rituximab/eculizumab in highly sensitized recipients with cPRA >50–80%) prevents hyperacute rejection.
- **Cold Ischemic Time vs. Ex-Vivo Normothermic Perfusion & DCD Hearts:**
  - **Traditional Cold Static Storage:** Target cold ischemic time **less than 4 hours** (prolonged ischemia >4 to 6 hours sharply increases **Primary Graft Dysfunction [PGD]** and 1-year mortality).
  - **Donation After Circulatory Death (DCD) and Ex-Vivo Perfusion ("Heart-in-a-Box"):** Controlled temperature preservation (SherpaPak) and ex-vivo normothermic machine perfusion (**TransMedics Organ Care System [OCS Heart] — EXPAND Trial** and the randomized **DCD Heart Trial**, *NEJM* 2023) or **Thoracoabdominal Normothermic Regional Perfusion (TA-NRP)** allow safe transplantation of **DCD hearts** and extended-criteria/long-distance (>4–6 hour) donor hearts, **expanding the donor pool by 20 to 30 percent with 6-month and 1-year survival equivalent to traditional brain-dead (DBD) donors**.

Post-Transplant Timeline	Dominant Complications	Key Diagnostic / Surveillance Modality	First-Line Management Strategy
Immediate (0 to 30 Days)	**Primary Graft Dysfunction (PGD)** & Acute RV Failure; Hyperacute rejection	Echocardiography + RHC hemodynamics	Inotropes, **inhaled NO**, and early **VA-ECMO** for severe PGD

Post-Transplant Timeline	Dominant Complications	Key Diagnostic / Surveillance Modality	First-Line Management Strategy
Early (1 Month to 1 Year)	**Acute Cellular Rejection (ACR — T-cell)** & **Antibody-Mediated Rejection (AMR — DSA/C4d)**; Opportunistic infections (**CMV, Pneumocystis**)	**Endomyocardial Biopsy (EMB — ISHLT Grade 0R to 3R; pAMR 0 to 3)** OR non-invasive **Donor-Derived Cell-Free DNA (dd-cfDNA) & GEP (AlloMap)**	**ACR (>=2R):** High-dose **IV Methylprednisolone** (+ ATG if hemodynamic compromise); **AMR:** Steroids + **Plasmapheresis + IVIG + Rituximab/Bortezomib**
Late (> 1 Year to 10+ Years)	**Cardiac Allograft Vasculopathy (CAV)**, **Malignancy** (skin cancer, PTLD), & CNI nephrotoxicity	Annual **Coronary Angiography + IVUS** (intimal thickening >=0.5 mm), **CCTA**, or **Quantitative Stress PET (MFR)**	**Universal Upfront Statin (Pravastatin/Simvastatin — Class I)** + switch MMF to **mTOR Inhibitor (Sirolimus / Everolimus — Class IIa)**

IV POST-TRANSPLANT IMMUNOSUPPRESSION, DENERVATED PHYSIOLOGY AND COMPLICATIONS

- **Standard Maintenance Triple Immunosuppression:**
  - **Calcineurin Inhibitor (CNI — Backbone): Tacrolimus** (preferred over Cyclosporine due to lower acute rejection rates, less hypertension/dyslipidemia, and absence of gingival hyperplasia/hirsutism; causes tremor, post-transplant diabetes, and nephrotoxicity).
  - **Antimetabolite (Purine Synthesis Inhibitor): Mycophenolate Mofetil (MMF)** or Enteric-Coated Mycophenolate Sodium (replaced by **Proliferation Signal / mTOR Inhibitors [Everolimus or Sirolimus]** after 3 to 6 months in patients who develop **CAV, CNI nephrotoxicity, or post-transplant malignancy**; note that mTOR inhibitors must **not** be started immediately post-op because they impair sternal wound healing and cause pericardial effusions).
  - **Corticosteroids:** Intravenous Methylprednisolone intraoperatively, followed by oral **Prednisone** tapered off over **6 to 12 months** in rejection-free recipients.
  - **Mandatory Universal Co-Medications: Statins** (initiated in **all** recipients at 1 to 2 weeks post-transplant **regardless of cholesterol levels [Class I]** because randomized trials with **Pravastatin and Simvastatin** proved reductions in **acute rejection, CAV, and 1-year mortality**), plus **Valganciclovir** (for CMV prophylaxis) and **Trimethoprim-Sulfamethoxazole** (for *Pneumocystis jirovecii* and *Toxoplasma* prophylaxis).
  - **Physiology and Pharmacology of the Surgically Denervated Heart (Crucial Exam Concept):**
  - **Loss of Efferent Vagal and Sympathetic Innervation:** Because the donor heart lacks parasympathetic vagal tone, the **resting sinus heart rate is elevated at 90 to 110 bpm** with loss of respiratory sinus arrhythmia. During exercise, heart rate rises **slowly over 5 to 10 minutes** (driven purely by **circulating adrenal catecholamines** rather than immediate neural sympathetic discharge) and decelerates slowly during recovery.
  - **Absence of Angina During Myocardial Ischemia:** Because afferent cardiac sympathetic pain fibers are transected, patients with **Cardiac Allograft Vasculopathy (CAV) or acute MI typically do NOT experience chest pain (angina)**, presenting instead with **silent heart failure, dyspnea, syncope, ventricular arrhythmias, or sudden death** (partial sympathetic reinnervation may occur in 30 to 40 percent after 3 to 5 years).
  - **Altered Drug Responses in the Denervated Heart:**
  - **Atropine and Digoxin (Vagotonic Effect): Completely INEFFECTIVE** for increasing or slowing the donor sinus node / AV node because the vagus nerve is disconnected from the donor heart (if the native recipient right atrial cuff remains in a biatrial anastomosis, Atropine speeds only the native P wave, not the conducted donor heart rate). **Use Isoproterenol, Epinephrine, or Terbutaline/Theophylline for bradycardia.**
  - **Adenosine:** Exhibits **marked denervation supersensitivity (3- to 5-fold exaggerated effect)**, causing prolonged ventricular asystole; if used, start at a **fraction of the normal dose (1.5 to 3 mg)**.
  - **Cardiac Allograft Vasculopathy (CAV — The Leading Cause of Late Graft Loss and Death After Year 1):** An immunologically mediated pan-arteritis characterized by **diffuse, concentric fibrous intimal hyperplasia** along the entire length of both epicardial and intramyocardial coronary vessels (unlike focal, eccentric lipid-rich atherosclerotic plaques, and typically sparing the native calcium). Because percutaneous stenting is only palliative, prevention relies on **universal Statins (Class I)**, **Diltiazem/Vitamins C & E**, and **conversion from MMF to Sirolimus or Everolimus (mTOR inhibitors — Class IIa)**, with **re-transplantation** reserved for severe ISHLT Grade 3 CAV with graft dysfunction.
  - **ISHLT Survival Outcomes:** Contemporary adult **1-year survival approaches 90 to 91 percent**, **overall median survival is 12.5 to 13 years**, and **conditional median survival for recipients who survive the first post-operative year exceeds 15 years**.

KEY REFERENCES

- **Mehra MR, Canter CE, Hannan MM, et al. (ISHLT Consensus):** The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: A 10-year update, *Journal of Heart and Lung Transplantation*, 2016.
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