Heart transplantation has evolved as the "gold standard" therapy, with median survival exceeding 10 years, for patients with endstage heart failure (HF). Advancements in the fields of immunosuppression, infection prophylaxis, and surgical techniques have transformed heart transplantation from what was once considered an experimental intervention into a routine treatment. The number of heart transplants reported to the International Society of Heart and Lung Transplantation registry worldwide has been 3,500–4,000 annually, but has not been increased over the past 2 decades because of donor shortage despite the growing number of patients with HF. This imbalance between the supply of donor hearts and the demand of patients with endstage HF has led to increased use of mechanical circulatory support as destination therapy, because the supply of mechanical devices is virtually unlimited. Although mechanical circulatory support technology is improving, heart transplantation remains the preferred treatment for many patients because of major complications, such as stroke, bleeding and infection, and because of limited quality of life related to the driveline and the need for battery change. Therefore, significant efforts have been made to maximize the number of heart transplants and to ensure good outcomes. (Circ J 2013; 77: 1097–1110)

**Key Words:** Endstage heart failure; Heart transplantation; Organ procurement; Transplant center; Ventricular assist devices

The number of patients with heart failure (HF) is increasing. Advanced HF is associated with increased morbidity and mortality, need for recurrent hospitalization, and a decrease in quality of life (QOL). Over the decades, significant advancements in HF treatment have been made, including pharmacological therapy, biventricular pacers/implantable cardioverter defibrillator, ventricular assist devices (VADs)/total artificial heart (TAH) and heart transplantation. Heart transplantation has evolved as the "gold standard" therapy, with median survival exceeding 10 years for patients with endstage HF. Advancements in the fields of immunosuppression, infection prophylaxis, and surgical techniques have transformed heart transplantation from what was once considered an experimental intervention into a routine treatment.

The number of heart transplants reported to the International Society for Heart and Lung Transplantation (ISHLT) registry worldwide has been 3,500–4,000 annually and it has not been increased over the past 2 decades, because of donor shortage despite the growing number of HF patients. This imbalance between the supply of donor hearts and the demand of patients with endstage HF has led to increased use of mechanical circulatory support as destination therapy, because the supply of mechanical devices is virtually unlimited. Although mechanical circulatory support technology is improving, heart transplantation remains the preferred treatment for many patients because of major complications, such as stroke, bleeding and infection, and because of limited QOL related to the driveline and need for battery change. Therefore, significant efforts have been made to maximize the number of heart transplants and to ensure good outcomes.

**US Federal and Non-Federal Agencies Overseeing the Heart Transplant System**

The field of transplantation is one of the most regulated areas of health care (Figure). In the United States, both state and federal legislation has been put in place to provide the safest and most equitable system for allocation, distribution and transplantation of donated organs. The Health Resources and Services Administration (HRSA) is the federal agency with responsibility for overseeing the transplant system. The following federal agencies also play a part in this lifesaving process: Centers for Medicare and Medicaid Services (CMS), Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH), Agency for Healthcare Research and Quality (AHRQ), and Food and Drug Administration (FDA).

**Department of Health and Human Services (HHS)**

The HHS is the United States government’s principal agency for protecting the health of all Americans and providing essential human services. The Department’s programs are administered by 11 operating divisions, which include HRSA, CMS, CDC, NIH, AHRQ and FDA. The HHS administers more grant dollars than all other federal agencies combined.
The CMS (Centers for Medicare and Medicaid Services) is a US federal agency that administers Medicare, Medicaid, and the State Children’s Health Insurance Program. Medicare program is the nation’s largest health insurer. Medicare and Medicaid together provide healthcare insurance for 1 in 4 Americans.

Organ Procurement and Transplantation Network (OPTN)
The OPTN is a nonprofit organization under federal contract. The primary purposes of the OPTN are to operate and monitor an equitable system for allocating organs donated for transplantation; maintain a waiting list of potential recipients; match potential recipients with organ donors according to established medical criteria for allocation of organs and, to the extent feasible, for listing and de-listing transplant patients; facilitate the efficient, effective placement of organs for transplantation; and increase organ donation.

United Network for Organ Sharing (UNOS)
UNOS is a private, nonprofit, scientific and educational organization that administers the OPTN under contract with HRSA.

Scientific Registry of Transplant Recipients (SRTR)
The SRTR is a national database of transplantation statistics. Founded in 1987, the registry exists to support ongoing evaluation of the scientific and clinical status of solid organ transplantation, including kidney, heart, liver, lung, intestine, and pancreas. Data in the registry are collected by the OPTN from hospitals and organ procurement organizations across the country.

Organ Procurement Organizations (OPOs)
OPOs are responsible for 2 main functions within their designated service area: (1) increasing the number of registered donors, and (2) coordinating the donation process when actual donors become available. There are 58 OPOs in the United States. When donors become available, OPOs evaluate the potential donors, check the deceased’s state donor registry, discuss donation with family members, contact the OPTN and run a match list and arrange for the recovery and transport of donated organs. They also provide bereavement support for donor families and volunteer opportunities for interested individuals. OPOs must be certified by the CMS and abide by CMS regulations.

The Joint Commission
The Joint Commission is an independent, nonprofit organization that accredits and certifies healthcare organizations and programs in the United States. The Joint Commission accreditation and certification is recognized nationwide as a symbol of quality that reflects an organization’s commitment to meeting certain performance standards.

Heart Transplant Center
It is mandatory for hospitals that are allowed to perform heart transplantation to meet certain criteria to ensure good outcomes. Each country has to have fair and justifiable criteria to qualify or disqualify hospitals as a heart transplant center. In particular, because of the donor shortage, only a limited number of centers should perform heart transplantation in order to achieve good outcomes. However, opportunities should be granted to new centers if they meet the criteria, and, at the same time, active centers should be inactivated if they no longer meet criteria.

The rule published on March 30, 2007 establishes Medicare conditions of participation (CoP), requirements of approval and reapproval of transplant centers to perform organ trans-
plants. This rule sets forth clear expectations for safe, high-quality transplant service delivery in Medicare-participating facilities.

In order to be granted approval from the CMS to provide transplant services, a transplant center must:
- be located within a hospital that has a Medicare provider agreement
- meet the CoP of the final rule
- meet all hospital CoP.

**CoP**

- OPTN membership
- Notification to CMS: transplant center must notify CMS immediately of any significant changes related to the center’s transplant program or changes that would alter elements in the approval/reapproval application, such as:
  - change in key staff members of the transplant team
  - decrease in the center’s volume or survival rates
  - termination of an agreement between the hospital and an OPO for the recovery and receipt of organs
  - inactivation of the transplant center.
- Patient selection criteria must:
  - ensure fair and non-discriminatory distribution of organs
  - include a psychosocial evaluation
  - include documentation in the patient’s medical record that the candidate’s blood type has been determined on at least 2 separate occasions
  - include documentation in the patient’s medical record of the patient selection criteria used.
- Organ recovery and receipt
  - Written protocols for deceased organ recovery and receipt to validate donor-recipient matching of blood types and other vital information.
  - The transplanting surgeon at the transplant center is responsible for ensuring medical suitability of donor organs for transplantation into the intended recipient.
- Organ recovery: when an intended transplant recipient is known, the organ recovery team must review and compare donor data with the recipient blood type and other vital information before organ recovery takes place.
  - Organ receipt: when an organ arrives at the center, the transplanting surgeon and at least 1 licensed healthcare professional must verify that the donor’s blood type and other vital information is compatible with transplantation of the intended recipient prior to transplantation.
  - Waitlist management: transplant center must:
    - update waitlist patients’ clinical information on an ongoing basis
    - remove patients from the center’s waitlist if a patient receives a transplant or dies, or if there is any other reason why the patient should no longer be on a center’s waitlist
    - notify the OPTN no later than 24 h after a patient’s removal from the center’s waitlist.
- Patient’s record must include:
  - notification of placement on the center’s waitlist; the center’s decision not to place the patient on its waitlist; or the center’s inability to make a determination regarding the patient’s placement on its waitlist because further clinical testing or documentation is needed
  - notification of removal from waitlist for reasons other than transplantation or death within 10 days
  - documentation of multidisciplinary patient care planning during the pretransplant period and multidisciplinary discharge planning for post-transplant care.
- Social services: transplant center must make available social services, furnished by qualified social workers, to transplant patients and their families.
- Nutritional services: nutritional assessments and diet counseling services furnished by a qualified dietitian must be available to all transplant patients and living donors.
- Quality assessment and performance improvement (QAPI): transplant center must have data-driven QAPI programs to monitor and evaluate performance of all transplantation services.
- Human resources
  - Director of a transplant center: transplant center must be under the general supervision of a qualified transplant surgeon or a qualified physician-director.

### Table 1. Membership Criteria for Primary Heart Transplant Surgeon

<table>
<thead>
<tr>
<th>Membership Criteria</th>
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<tbody>
<tr>
<td>1. On site</td>
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<tr>
<td>2. Certified by the American Board of Thoracic Surgery or the foreign equivalent</td>
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<tr>
<td>3. Thoracic Surgery Boards pending</td>
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<tr>
<td>4. Cardiothoracic Surgery Residency</td>
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</tr>
<tr>
<td>a. Primary surgeon or 1st assistant on 20 or more heart and/or heart/lung transplants</td>
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<tr>
<td>b. Primary surgeon or 1st assistant on 10 or more heart or heart/lung procurements</td>
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<tr>
<td>c. Involved in all levels of pre-, peri-, and postoperative patient care within the last 2 years</td>
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<tr>
<td>d. Training program approved by American Board of Thoracic Surgery</td>
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<tr>
<td>5. 12-month Heart Transplant Fellowship</td>
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</tr>
<tr>
<td>a. Primary surgeon or 1st assistant on 20 or more heart and/or heart/lung transplants</td>
<td></td>
</tr>
<tr>
<td>b. Primary surgeon or 1st assistant on 10 or more heart or heart/lung procurements</td>
<td></td>
</tr>
<tr>
<td>c. Involved in all levels of pre-, peri-, and postoperative patient care within the last 2 years</td>
<td></td>
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<tr>
<td>d. Training program approved by American Board of Thoracic Surgery</td>
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<tr>
<td>6. Experience (Post Fellowship)</td>
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<tr>
<td>a. Primary surgeon or 1st assistant on 20 or more heart and/or heart/lung transplants over a minimum of 2 years and a maximum of 5 years. Of these 20 transplants, at least 15 were performed as primary surgeon</td>
<td></td>
</tr>
<tr>
<td>b. Primary surgeon or 1st assistant on 10 or more heart or heart/lung procurements</td>
<td></td>
</tr>
<tr>
<td>c. Involved in all levels of pre-, peri-, and postoperative patient care within the last 2 years</td>
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</table>
Recipient Selection

The evaluation of patients with endstage heart disease and the selection of potential candidates for cardiac transplantation must be undertaken by a multidisciplinary committee according to CMS and UNOS guidelines to ensure an equitable, objective, and medically justified allocation of the limited donor organs to patients with the greatest chance of postoperative survival and rehabilitation.4

The perception of the irreversibility of advanced HF is changing because of tailored medical therapy, high-risk revascularization procedures, and newer antiarrhythmic pharmacologic agents, as well as implantable defibrillators and biventricular pacing. Caution should be exercised in judging prognosis of these patient subgroups, and a period of observation, intense pharmacologic therapy, surgical procedure such ventricular restoration, and/or mechanical support by VADs should be undertaken before heart transplantation is considered.6,8,12

Evaluation of the Potential Cardiac Transplant Recipient

The complexity of the recipient evaluation mandates a team approach. The initial evaluation involves a history and physical examinations, 12-lead ECG, Holter monitor, and echocardiography, assessment of heart function, and cardiopulmonary exercise testing (peak VO₂max).13,14

In addition, a respiratory exchange ratio >1.0 or achievement of an anaerobic threshold at 50–60% of VO₂max, is necessary to avoid underestimation of functional capacity.15 Right-sided heart catheterization should be performed at the transplanting center to evaluate the severity of HF, and thus the status level for transplant, and to evaluate for the presence of pulmonary hypertension. Coronary cineangiography, a position-emission tomographic scan, a thallium-201 redistribution study, or a cardiac magnetic resonance imaging (MRI) study should be reviewed for revascularization if sufficient viability is found.15,16 Endomyocardial biopsy should be performed to assess questionable HF etiology, assist in therapeutic decision making, and exclude diseases such as amyloidosis.

Psychological Evaluation

A neuropsychiatric evaluation should be performed so that the candidate can understand the difficulties experienced during the waiting period, recovery, and postoperative period; understand the rationale of the anti-rejection medications; and understand the rules for living with a new heart. An experienced social worker should explain the need for adequate social and financial support. All patients are screened for smoking and the use of alcohol and other recreational drugs.

Indications for Cardiac Transplantation

In many centers, the standard guidelines are maintained even though each transplant center can have their own criteria to include heart transplantation patient. Table 2 describes the indications and contraindications for cardiac transplantation.

Management of the Potential Cardiac Recipient

Pharmacologic Bridge to Transplantation

Critically compromised patients require intravenous catecholamine dopamine as a parenteral positive inotrope, but at moderate to high dose this evokes considerable systemic vasoconstriction. In candidates in whom an inotropic infusion has progressed to higher doses, combinations of dobutamine with milrinone are used.

Mechanical Bridge to Transplantation

Placement of an intra-aortic balloon pump (IABP) may be necessary through the axillary artery as a bridge to cardiac transplantation17 in endstage HF patients who are refractory to initial pharmacologic measures.

The landmark Randomized Evaluation of Mechanical Assistance in Treatment of Chronic Heart Failure (REMATCH) trial provided evidence that LVAD support provided a statistically significant reduction in the risk of death from any cause when compared with optimal medical management.6

The newer axial flow and centrifugal VADs have been shown to provide significantly better survival and less adverse events
than first-generation VADs and their short- to mid-term survival rates are approaching those of heart transplantation.

In a randomized trial, Slaughter et al. investigated patients with advanced HF who were ineligible for transplantation, in a 2:1 ratio, to undergo implantation of a continuous-flow device (134 patients) or pulsatile-flow device (66 patients). They concluded that the primary composite endpoint (at 2 years, survival free from disabling stroke and reoperation to repair or replace the device) was achieved in more patients with continuous-flow devices than with pulsatile-flow devices (46% vs. 11%; P<0.001), and patients with continuous-flow devices had superior actuarial survival rates at 2 years (58% vs. 24%, P=0.008), significantly improved the QOL and functional capacity with less frequent adverse events and device replacements.

Fang et al. emphasized the true assistance of endstage HF by the newer machines such as continuous-flow VADs. They compared the REMATCH trial with the study done by Slaughter et al. and found significant improvement in the probability of survival associated with the continuous-flow device, which was double (at 2 years) than in the REMATCH trial (at 1 year).

Fang et al. also emphasized integrating the results of this study into clinical practice by making sure patients and physicians are aware that VAD therapy is available, effective, and safe for well-selected patients. They insist that delay in referral should not occur until surgical morbidity and mortality become prohibitive. Lessons from clinical experience and published reports support the notion that the optimal time for referral is most likely before the development of major complications of HF. Any patient in whom intravenous inotropic support is required should be considered a candidate for destination therapy. Third, the evaluation and care of these pa-

### Table 2. Indications and Absolute and Relative Contraindications for Cardiac Transplantation

**Acceptable candidates will have the following:**
- Maximal VO₂ <10 ml·kg⁻¹·min⁻¹ with achievement of anaerobic metabolism
- Severe ischemia consistently limiting routine activity not amenable to revascularization
- Recurrent symptomatic ventricular arrhythmia refractory to all accepted therapeutic modalities

**Probable candidates could have the following:**
- Maximal VO₂ <14 ml·kg⁻¹·min⁻¹ and major limitation of the patient’s daily activities
- Recurrent unstable angina not amenable to revascularization
- Unstable fluid balance/renal function not related to patient noncompliance with a regimen of weight monitoring, flexible use of diuretics and salt restriction
- NYHA class III–IV symptoms on optimal medical therapy and prognosis for 1-year survival <75%
- Heterotopic heart transplant
- Endstage heart disease not amenable to other medical or surgical therapy with irreversible pulmonary hypertension
- NYHA class III–IV symptoms on optimal medical therapy and prognosis for 1-year survival <75%
- No underlying pulmonary disease

**Absolute contraindications could be the following:**
- Major systemic disease
- Age inappropriateness (70–75 years old)
- Cancer in the past 5 years other than localized skin (not melanoma) or stage I breast or prostate
- Active smoker (<6 months since quitting)
- Active substance abuse
- HIV
- Severe local or systemic infection
- Severe neurologic deficit
- Major psychiatric illness or active substance abuse that cannot be managed sufficiently to allow post-transplant care and safety

**Relative contraindications could be the following:**
- Severe pulmonary hypertension with PAS >60 mmHg, TPG >15 mmHg, PVR >3.5 Wood units, irreversible with milrinone
- Pulmonary dysfunction with FVC and FEV₁ <40% predicted, especially with intrinsic lung disease on imaging
- Acute pulmonary thromboembolism
- Morbid obesity (>140% ideal body weight. For males, 106 lbs. for first 5 feet of height then 6 lbs. for each additional inch. For women, 100 lbs. for first 5 feet of height then 5 lbs. for each additional inch)
- Irreversible hepatic dysfunction with bilirubin >2.5 mg/dl and/or transaminases > twice normal, or cirrhosis on biopsy
- Irreversible renal dysfunction with creatinine clearance <40–50 ml/min or ERPF <200 ml/min
- Documented severe peripheral or cerebrovascular disease
- Coexisting neoplasm or history of neoplasm other than skin within 5 years
- Insulin-requiring diabetes mellitus with end-organ damage
- Active peptic ulcer disease
- Current or recent diverticulitis
- Cachexia
- Inability to make a strong commitment to transplantation
- Absence of adequate external psychosocial support on either short-term or long-term basis

ERPF, effective renal plasma flow; FEV₁, forced expiratory volume in 1s; FVC, forced vital capacity; HIV, human immunodeficiency virus; NYHA, New York Heart Association; PAS, pulmonary arterial stenosis; PVR, peripheral vascular resistance; TPG, transpulmonary gradient.
Table 3. Current Recipient Status Criteria of the UNOS and Medical Management of the Cardiac Donor

<table>
<thead>
<tr>
<th>UNOS Status IA</th>
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<tbody>
<tr>
<td>A. Patients who require mechanical circulatory assistance with one or more of the following devices:</td>
</tr>
<tr>
<td>1. Total artificial heart</td>
</tr>
<tr>
<td>2. Left and/or right ventricular assist device implanted for 30 days or less</td>
</tr>
<tr>
<td>3. Intra-aortic balloon pump</td>
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<tr>
<td>4. Extracorporeal membrane oxygenator (ECMO)</td>
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<tr>
<td>B. Mechanical circulatory support for more than 30 days with significant device-related complications</td>
</tr>
<tr>
<td>C. Mechanical ventilation</td>
</tr>
<tr>
<td>D. Continuous infusion of high-dose inotrope(s) in addition to continuous hemodynamic monitoring of LV filling pressures</td>
</tr>
<tr>
<td>E. Life expectancy without transplant less than 7 days</td>
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<table>
<thead>
<tr>
<th>UNOS Status IB</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. A patient who has at least one of the following devices or therapies in place:</td>
</tr>
<tr>
<td>1. Left and/or right ventricular assist device implanted for more than 30 days</td>
</tr>
<tr>
<td>2. Continuous infusion of intravenous inotropes</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>UNOS Status II</th>
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<tbody>
<tr>
<td>All other waiting patients who do not meet Status Ia or Ib criteria</td>
</tr>
</tbody>
</table>

Medical management of the cardiac donor

I. Conventional management, before the initial echocardiogram

A. Adjust volume status (target central venous pressure 6–10 mmHg)

B. Correct metabolic perturbations, including

1. Acidosis (target pH 7.40–7.45)
2. Hypoxemia (target PO2 >80 mmHg, O2 saturation >95%)
3. Hypercarbia (target PCO2 30–35 mmHg)
4. Correct anemia (target hematocrit 30%, hemoglobin 10 g/dl)

D. Adjust inotropes to maintain mean arterial pressure at 60 mmHg

E. Target=dopamine <10 μg·kg⁻¹·min⁻¹ or dobutamine <10 μg·kg⁻¹·min⁻¹

II. Obtain an initial echocardiogram

A. Rule out structural abnormalities (substantial LV hypertrophy, valvular dysfunction, congenital lesions)

B. If LV ejection fraction is 45%, proceed with recovery (consider aggressive management as shown below to optimize cardiac function before recovery) with final evaluation in the operating room

C. If LV ejection fraction is <45%, aggressive management with placement of a pulmonary arterial catheter and hormonal resuscitation is strongly recommended

III. Hormonal resuscitation

A. Triiodothyronine (T3): 4-μg bolus, then continuous infusion at 3μg/h

B. Arginine Vasopressin: 1-unit bolus, then continuous infusion at 0.5–4 units/h, titrated to a systemic vascular resistance of 800–1,200 dyne·s·cm⁻⁵

C. Methylprednisolone: 15 mg/kg bolus

D. Insulin: 1 unit/h minimum; titrate to maintain blood sugar at 120–180 mg/dl

IV. Aggressive hemodynamic management

A. Initiated simultaneously with hormonal resuscitation

B. Placement of pulmonary artery catheter

C. Duration of therapy 2h

D. Adjustment of fluids, inotropes, and pressors every 15 min, based on serial hemodynamic measurements to minimize use of β-agonists and meet the following target (Papworth) criteria

1. Mean arterial pressure >60 mmHg
2. Central venous pressure 4–12 mmHg
3. Pulmonary capillary wedge pressure 8–12 mmHg
4. Systemic vascular resistance 800–1,200 dyne·s·cm⁻⁵
5. Cardiac index >2.4 L·min⁻¹·m⁻²
6. Dopamine <10 μg·kg⁻¹·min⁻¹ or dobutamine <10 μg·kg⁻¹·min⁻¹

LV, left ventricular; UNOS, United Network for Organ Sharing.

tients requires special expertise. Identifying the optimal timing for implantation in an individual patient’s course of progressive HF is both an art and a science. The American Board of Internal Medicine’s subspecialty of Advanced Heart Failure and Transplantation Cardiology and the Joint Commission’s certification for destination therapy were created with this in mind.

Fang et al conclude that although the selection of patients, device durability and cost, and other considerations remain challenging in this rapidly evolving field, there is little doubt
that LVADs are a viable and important option for patients with medically refractory, advanced HF.

The ENDURANCE clinical trial included the use of the HeartWare® Ventricular Assist System as a destination therapy in advanced HF patients (450 patients enrolled at 50 US hospitals). The study is ongoing to investigate the primary endpoint, which is stroke_free survival at 2 years. Secondary endpoints include incidence of bleeding, major infection and device failure, as well as health and functional status improvement (clinical trial.gov).

The ADVANCE clinical trial was designed to evaluate the HeartWare Ventricular Assist System as a bridge to heart transplantation for patients with endstage HF (n=140) who were followed for ≥180 days after implant or until cardiac transplantation, device explant for recovery, or death. Results showed 91% better survival at 180 days and 84% better survival at 360 days with the HeartWare VAD compared with INTERMACS VAD data (n=499).

TAH Because the TAH replaces both ventricles, it has the potential advantage of eliminating problems commonly seen with LVADs and BiVADs, such as right-sided HF, valvular regurgitation, cardiac arrhythmias, ventricular clots, intraventricular communications, and low blood flow. A patient’s candidacy for the TAH should be scrutinized prior to placement of the device, which cannot be weaned.

Recipient Prioritization for Transplantation

The prioritization of appropriate recipients for transplantation is based on survival and the QOL that is expected to be gained compared with maximal medical and surgical alternatives available. Geographic distance between donor and potential recipient is also considered. Patients considered for transplantation should be examined every 3 months for reevaluation of recipient status. Yearly right-sided heart catheterization is indicated for all candidates on the waiting list and in selected patients with pulmonary hypertension who were rejected earlier. Table 3 describes the UNOS status criteria for cardiac transplant recipients.

Luminex Virtual Crossmatching

Anti-human leukocyte antigen (HLA) antibodies can be detected before transplantation using different techniques. Complement-dependent lymphocytotoxicity assays are used widely to measure the panel-reactive antibody (PRA), and for crossmatching purposes. Newer assays using solid-phase flow techniques feature improved specificity. They offer detailed information concerning antibody specificities, which may lead to improvements in donor-recipient matching. Allosensitization prolongs the wait time for transplantation and increases the risk of post-transplant complications and death. It is of vital importance to decrease the anti-HLA antibodies in sensitized transplant candidates.

Histocompatibility testing can identify appropriate donor-recipient pairs to achieve successful transplantation. Pretransplant crossmatching identifies recipient serum antibodies that react with donor antigens, indicating the concept of allosensitization. Kerman described a method of understanding the sensitized patient to determine whether these antibodies may increase the risk of post-transplant adverse outcomes, as is the case with anti-HLA immunoglobulins.

Anti-HLA antibodies are directed to donor major histocompatibility complex (MHC) classes I and II HLA antigens that are expressed on allograft endothelial cells. The risk of early graft failure after transplant is higher in the presence of a positive crossmatch with donor HLA antigens and is related to circulating recipient anti-donor antibodies. To detect allosensitization, transplant candidates undergo testing that exposes HLA antigens from random individuals to the recipient’s serum through a variety of different techniques and this is called as a PRA test.

The rationale for PRA testing in cardiac transplant candidates comes from prior published results and experiences in kidney transplantation, showing an inverse relationship between PRA level and allograft survival. The initial step in managing allosensitized transplant candidates is to avoid further exposure to foreign human antigens by minimizing the transfusion of blood products. Use of the virtual crossmatch has been applied in recent years in heart transplantation. The utility of the virtual crossmatch is the provision of the opportunity to expand the geographic area from which organs with limited permissible cold ischemia time can be recovered. It reduces both waiting time and deaths on the waiting list, and is a good indicator of the risk of antibody-mediated rejection. There are many reports of the feasibility and utility of the virtual crossmatch that is determined from solid-phase immunoassays (SPI). Vaidya established SPI values that yielded a high correlation between predicted and actual crossmatches. The basis of this was a correlation between the strength of antibodies and the reactivity strength determined by SPI. However, these correlations are optimized when the strength of donor-specific antibodies (DSA) and not third-party-specific antibody is used for predicting the crossmatch outcome.

It has been demonstrated by others that bead-based fluorometric assays are more sensitive than colorimetric enzyme-linked immunosorbent assays (ELISA). It has been shown that the presence of DSA is detected by Luminex-based testing nearly twice as often as by enzyme-linked immunosorbent assay (ELISA).

Zachary et al reported data indicating that the identity and strength of DSA defined with solid-phase phenotype panels significantly correlates with the outcome of both cytotoxic (CDC; r 0.83) and flow cytometric (r 0.85) crossmatches. Based on the threshold established by these correlations, they were able to predict the results of CDC and flow cytometric crossmatches in 92.8 and 92.4% of cases, respectively. The correlations with single-antigen panels were substantially lower (82.6–47.9%). They demonstrated that adding additional information to the solid-phase results can increase the frequency of correct crossmatch prediction and described the process of validity and reliability of performing a virtual crossmatch from Luminex-based assays (92.1% correct predictions) and ELISA microchip assay.

Smith et al presented a developed method of detecting C4d-fixing HLA antibodies on Luminex beads. Pretransplant serum from 565 cardiac transplant patients was retrospectively tested for the presence of HLA antibodies using CDC, HLA-coated Luminex beads and C4d deposition on Luminex beads. The results correlated with graft survival. In 5 of 565 patients, CDC-positive DSA were detected before their transplant, and this number was increased by 19 using Luminex beads. The 1-year survival of CDC−ve/Luminex +ve patients with DSA (n=19) was 42% compared with 77% for CDC−ve/Luminex +ve without DSA (n=39, P=0.0039). They showed that fixation of C4d (22/67 Luminex positive sera) had a negative effect on graft outcome; 1-year graft survival was 20% for C4d+ve/DSA−ve (n=11), 91% for C4d+ve/DAS−ve (n=11), 54% for C4d−ve/DAS−ve (n=13), and 75% for C4d−ve/DAS−ve (n=32), compared with 75% for antibody-negative patients (P=0.0002). Smith et al concluded that detection of Luminex+
ve DSA in pretransplant serum provides a powerful negative predictor of graft survival, especially if they bind C4d.

Worsley et al from the Johannesburg Renal Transplantation Program retrospectively evaluated the use of Luminex anti-HLA antibody detection technology and compared it with flow cytometric crossmatching to predict graft outcome in renal transplant patients. They investigated 64 recipients who were crossmatched against multiple donors during their routine work-up for transplant (111 crossmatches); 17 of these patients received transplants during the study period. Anti-HLA antibody detection was performed using Luminex technology and the results were compared with the flow cytometric crossmatch results for short-term graft success: the sensitivity and specificity of Luminex virtual crossmatching was 85.7% and 90.7% for the T-cell crossmatch and 100% and 87.2% for the B-cell crossmatch. Their results showed that both the sensitivity and specificity of Luminex for predicting short-term graft success was 100%. They recommended incorporation of single-antigen Luminex methodology into the routine work-up algorithm of renal transplant recipients in South Africa.

The critical elements of a virtual crossmatch are thorough analysis of antibody screening test results, accurate determination of antibody specificity and strength, and knowledge of the factors that may affect test outcome. Careful analysis of the factors that may influence the crossmatch outcome is to be considered.

**Donor Selection**

A brain-dead individual identified as a potential cardiac donor undergoes a rigorous 3-phase screening regimen. UNOS screens for information regarding the patient’s age, height and weight, sex, ABO blood type, hospital course, cause of death, and routine laboratory data, including cytomegalovirus (CMV), human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) serologies. Cardiac surgeons or cardiologists perform the secondary screening for potential contraindications, determination of the hemodynamic support necessary to sustain the donor, and review of the ECG, chest X-ray, arterial blood gas determination, and echocardiogram. The final screening of the donor is done by the cardiac surgical team during organ procurement. Direct visualization of the heart is performed for evidence of ventricular or valvular dysfunction, previous infarction, or myocardial contusion secondary to closed-chest compressions or blunt chest trauma. The coronary arterial tree is palpated for gross calcifications indicative of atherosclerosis. After direct examination and unremarkable findings, the recipient hospital is notified. The procurement surgeons proceed with donor cardiectomy, usually in conjunction with multiorgan procurement. Table 3 describes the medical management of the cardiac donor.

**Expanded Donor Criteria and Alternate Listing**

An alternate recipient list is being used by some centers to match certain excluded recipients from a standard list with marginal donor hearts that otherwise would go unused.

Zaroff et al describe detailed recommendations on maximizing use of organs recovered when donors may be substantially smaller than the recipients, donors with coronary artery disease (CAD) that may require coronary artery bypass grafting, have left ventricular dysfunction, or donors from older age groups.

Hsu et al showed 30-day mortality rate results of 5%, and 1- and 5-year survival rates of 87% and 83%, respectively, in 79 heart transplant patients with 58% marginal donors and recipients in their hospital from 1993 to 1998. They suggested that heart transplantation may be performed in marginal recipients and donors, with acceptable operative mortality.

Laks et al reported an alternate use of an adult recipient list: those who underwent transplantation (Group I), and another group of 401 contemporaneous recipients (Group II). Hearts were first offered to regularly listed patients. Survival for alternates at 90 days was 82% (vs 91%, P=0.04) and alternate listing did not independently predict early or late mortality. Late (>90 days) death rates per 1,000 person-months were 4.3 and 3.6 for groups I and II, respectively. They suggested that using 2 adult recipient lists facilitated allocation of unused donor organs and satisfactory survival.

Freimark et al showed unfavorable early outcomes for patients receiving hearts from alcoholic donors (>2 oz of pure alcohol daily for 3 or more months), suggesting the presence of a subclinical preoperative alcoholic cardiomyopathy and poor tolerance of rejection episodes.

**Donor-Recipient Matching**

The criteria for matching potential recipients with the appropriate donor are based primarily on ABO blood group compatibility and patient size to avoid fatal hyperacute rejection. Donor weight should be within 30% of recipient weight, except in pediatric patients. In cases of elevated pulmonary vascular resistance in the recipient (5–6 Wood units), a larger donor is preferred to reduce the risk of right ventricular (RV) failure that may occur in the early postoperative period. Although practices vary by transplant program, generally a prospective negative T-cell crossmatch between the recipient and donor sera is mandatory prior to transplantation. Retrospective studies by Jarcho et al have demonstrated that better matching at the HLA-DR locus results in fewer episodes of rejection and infection with an overall improved survival.

**Hemodynamic Management**

Transplantation necessitates transsection of antagonistic sympathetic and parasympathetic fibers of the autonomic nervous system. A denervated heart with altered physiology results, with increased intrinsic resting rate of 90–110 beats/min. The allograft relies on distant noncardiac sites as its source of catecholamines. Its response to stress such as hypovolemia, hypoxia, and anemia etc is somewhat delayed until circulating catecholamines can exert their positive chronotropic effect on the heart. The absence of a normal reflex tachycardia in response to venous pooling may account for frequent orthostatic hypotension in transplant patients. Carotid sinus massage, Valsalva maneuver, and atropine will have no effect on sino-atrial node (SAN) firing or atrioventricular conduction.

**Routine Hemodynamic Management**

During the immediate postoperative period, donor myocardial performance is transiently depressed. Allograft injury associated with donor hemodynamic instability and the hypothermic, ischemic insult contribute to the reduced ventricular compliance and contractility in the newly transplanted heart. Abnormal atrial dynamics owing to the mid-atrial anastomosis exacerbate the reduction in ventricular diastolic loading. An infusion of epinephrine or dobutamine is routinely initiated in the operating room to provide temporary inotropic support. Cardiac denervation brings several consequences that may include a chronotropoe and an inotropic supersensitivity to exogenous catecholamines. Restoration of normal myocardial
function permits the cautious weaning of inotropic support within 2 to 4 days.

**Early Allograft Failure**

Early cardiac failure still accounts for up to 20% of perioperative deaths of heart transplant recipients. Most important etiologies are myocardial dysfunction owing to donor instability, pulmonary hypertension, ischemic injury during preservation, and acute rejection. Mechanical support with an IABP or VAD can be attempted in patients refractory to pharmacologic interventions with very high mortality. Chronic LV failure is frequently associated with elevated pulmonary vascular resistance. The donor right ventricle may be unable to overcome this increased afterload. Right-sided HF remains a leading cause of early mortality. Initial management involves the use of pulmonary vasodilators such as inhaled nitric oxide, nitroglycerin, or sodium nitroprusside. Pulmonary hypertension that is refractory to these vasodilators sometimes responds to prostaglandin E₂ or prostacyclin. Intra-aortic or pulmonary artery balloon counterpulsation and RVADs can be used in patients who are unresponsive to medical therapy.

**Arrhythmias**

Parasympathetic denervation causes a persistent increase in the resting heart rate and a loss of normal, rapid heart rate modulation, with elimination of the chronotropic effects of digoxin and atropine after heart transplantation. Sympathetic denervation causes a decrease and delay in exercise- or stress-induced augmentation of SAN automaticity, resulting in a decreased maximum heart rate with exercise.

Atrial fibrillation, atrial flutter, and other supraventricular arrhythmias have been reported in up to half of transplant recipients. Adequate heart rate is achieved with inotropic drug infusions and/or temporary epicardial pacing. Most bradyarrhythmias resolve over 1 to 2 weeks.

Sustained ventricular tachycardia and ventricular fibrillation presumably are responsible for a significant portion of the 10% of sudden and unexplained deaths in heart transplant patients.

**Systemic Hypertension**

Systemic hypertension should be treated to prevent unnecessary afterload stress on the allograft. In the early postoperative period, intravenous sodium nitroprusside or nitroglycerin usually is administered. Nicardipine infusion has been reported to control postoperative hypertension more rapidly and be superior to sodium nitroprusside in maintaining LV performance.

**Respiratory Management**

The respiratory management of the cardiac transplant recipient uses the same protocols followed after routine cardiac surgery.

**Renal Function**

Preoperative renal insufficiency because of chronic HF and the nephrotoxic effects of the calcineurin inhibitor (CNI), cyclosporine, place the recipient at increased risk of renal insufficiency. Acute CNI-induced renal insufficiency will resolve with a reduction in the dose. Concurrent administration of mannitol with cyclosporine may reduce its nephrotoxicity. Most centers administer a cytolytic agent in the immediate postoperative period and delay the initiation of CNI therapy.

**Outpatient Follow-up**

Prior to discharge, patients should receive comprehensive education about their medications, diet, exercise, and infection recognition. Close follow-up by an experienced transplant team is the cornerstone of successful long-term survival after cardiac transplantation. This comprehensive team facilitates the early detection of rejection, opportunistic infections, patient noncompliance, and adverse sequelae of immunosuppression. Clinic visits, which are scheduled routinely and concurrently with endomyocardial biopsies, include physical examination, a variety of laboratory studies, chest X-ray and ECG.

**Immunosuppressive Therapy**

The overwhelming majority of post-transplant deaths occur after 30 days and less than 10%. A planned immunosuppressive regimen would save many more lives than the perfect surgical technique or donor organ. Changes in immunosuppressive therapy have had a major effect on improving survival after heart transplantation as evidenced by the increasing number of deaths owing to rejection in recent years. Immunosuppressive regimens can be classified as induction, maintenance, or anti-rejection. Induction regimens provide intense early postoperative immune suppression, whereas maintenance regimens are used throughout the patient’s life to prevent both acute and chronic rejection.

**Induction Immunosuppressive Regimens**

Approximately 50% of heart transplant programs currently use a strategy of augmented immunosuppression, or induction therapy, during the early postoperative period. From the clinical perspective, the main advantages of induction therapy are to allow delayed initiation of nephrotoxic immunosuppressive drugs in patients with compromised renal function prior to or following surgery. It provides some flexibility with respect to early glucocorticoid weaning or use of glucocorticoid-sparing baseline regimens after transplantation.

**Interleukin (IL)-2 Receptor Antagonists**

Use of IL-2 receptor antagonists for induction therapy has increased, and these drugs are now used in 27% of patients undergoing heart transplantation. The currently available agent, basiliximab (Simulect), is a monoclonal antibody that selectively binds to the IL-2 receptor of T lymphocytes, blocking binding of IL-2 to the receptor complex, and exhibiting its immunosuppressive effects by inhibiting IL-2-mediated T-lymphocyte proliferation.

**Polyclonal Anti-Thymocyte Antibodies**

Polyclonal antibodies are derived by immunization of horses (ATGAM®, also called lymphocyte immune globulin) or rabbits (Thymoglobulin®) with human thymocytes. These combined agents are currently used in 23% of heart transplant recipients according to the most recent international transplant registry data.

**Muromonab-CD3 (OKT3)**

OKT3 is a murine monoclonal antibody that binds to the T-cell receptor-CD3 complex on the surface of circulating T cells. It exerts its immunosuppressive effects via a variety of mechanisms, including rapid T-cell depletion from the peripheral circulation after opsonization in
the liver and spleen, and modulation of the T-cell receptor-CD3 antigen recognition complex and thereby blocking the immunologic function of these cells. However, because of these adverse effects and the availability of alternate agents, the use of OKT3 as induction therapy in heart transplantation significantly declined between 1997 and 2007 and is now used in less than 1% of heart transplant recipients.

**Alemtuzumab (Campath-1H)** This is a humanized rat monoclonal antibody that targets the CD52 antigen expressed on both T and B cells. Campath may decrease the incidence of early (<12 months) acute cellular rejection.

**Maintenance Immunosuppressive Regimens**

The strategies and drugs used for immunosuppression have advanced significantly since the first heart transplant was performed in 1967. With the introduction of cyclosporine in 1983, significant advances have been made in moving from drugs that provide broad and nonspecific immunosuppression to newer agents that provide more targeted immunosuppression through selective inhibition of lymphocyte activation and proliferation. This selectivity has resulted in a marked increase in patient survival because of the decrease in the incidence of life-threatening opportunistic infections and rejection episodes.

Currently, the “standard” maintenance immunosuppression protocols known as triple therapy for heart transplantation include (1) CNI such as cyclosporine or tacrolimus, (2) antiproliferative agent such as azathioprine (AZA), mycophenolate mofetil, or rarely, cyclophosphamide, and (3) corticosteroids such as prednisone or prednisolone over the first year post-transplantation. Many centers also add an antilymphocyte antibody perioperatively, such as antithymocyte globulin (ATG), thymoglobulin, or rarely, cyclophosphamide, and (4) corticosteroids to create a quadruple-drug regimen.

In recent years, sirolimus (rapamycin) and everolimus (a derivative of rapamycin) have been introduced into clinical heart transplantation and they act by blocking several events downstream of the IL-2 receptor. In the setting of pretransplant renal insufficiency, a popular protocol that involves antilymphocyte antibody therapy in the interim, so-called sequential therapy, delays the initiation of the CNIs for 1–2 weeks postoperatively to allow renal function recovery and permits adequate immunosuppression with reduced doses of individual agents to minimize their toxicity.

**Hyperacute Rejection** Hyperacute rejection results from preformed DSA in the recipient. The onset of hyperacute catastrophic rejection occurs within minutes to several hours after transplantation. Gross inspection reveals a mottled or dark red, flaccid allograft, and histologic examination confirms the characteristic global interstitial hemorrhage and edema without lymphocytic infiltrate. Immunofluorescence techniques reveal deposits of immunoglobulins and complement on the vascular endothelium. Immediate plasmapheresis, intravenous immunoglobulin (IVIG), and mechanical support are instituted, and retransplantation may be the only successful strategy.

**Acute Rejection** Cardiac allograft rejection is the normal host response to cells not recognized as self. The vast majority of cases are mediated by the cellular limb of the immune response through a cascade of events involving macrophages, cytokines, and T lymphocytes. Humoral-mediated rejection (also called vascular rejection) is less common. The highest risk factors are allografts from younger and female donors, irrespective of recipient sex. Approximately 85% of episodes can be reversed with corticosteroid therapy alone.

**Diagnosis of Acute Rejection** Acute rejection reflects the greater risk during the first 6 months following transplanta-
Infectious Complications After Heart Transplantation

Transmission of infections such as CMV, Toxoplasma gondii, HBV, HCV, and HIV after organ transplantation are well documented.79,80

Specific Organisms Causing Infection Following Heart Transplantation

Bacteria Gram-negative bacilli, Escherichia coli and Pseudomonas aeruginosa, Gram-positive.78 Staphylococcus species have been shown to be the cause of the majority of infections.

Virus CMV remains the single most important cause of infectious disease morbidity and mortality in the heart transplant patient.81 CMV is indirectly associated with acute rejection episodes, acceleration of CAV, and post-transplant lymphoproliferative disease.81 Various regimens for CMV prophylaxis with ganciclovir are being used by different centers.82 The standard of care for symptomatic CMV disease is 2–3 weeks of intravenous ganciclovir at a dose of 5 mg/kg twice daily. Dosage adjustment for renal dysfunction is done carefully. Many centers add anti-CMV hyperimmune globulin to this regimen for tissue-invasive disease such as pneumonia. Preemptive treatment strategies use periodic surveillance using plasma polymerase chain reaction (PCR) and CMV antigenemia, a rapid diagnostic test that detects viral protein in peripheral blood leukocytes before clinical disease.83,84

Fungi Mucocutaneous candidiasis.

Candida Infection Aspergillus is the opportunistic pathogen with highest mortality and causes a serious pneumonia in 5–10% of recipients during the first 3 months after transplantation.85

Protozoa In heart transplant recipients, the reported incidence of Pneumocystis carinii pneumonia ranges from less than 1% to 10%.78,86

Toxoplasma gondii Infection Toxoplasmosis following heart transplantation is the result of reactivation of latent disease in the seropositive donor heart and because of the predilection of the parasite to invade muscle tissue. T. gondii usually causes central nervous system infections and is treated with pyrimethamine with sulfadiazine or clindamycin.

Chronic Complications After Heart Transplantation

Cardiac Allograft Vasculopathy

CAV is a unique and rapidly progressive form of atherosclerosis in transplant recipients. It is a leading cause of death in the first year post-transplantation,87,88 limiting long-term survival. It is characterized in its early stages by intimal proliferation and in its later stages by luminal stenosis of epicardial branches, occlusion of smaller arteries, and myocardial infarction.89 Angiographically detectable CAV is reported in 40–50% of patients by 5 years after transplantation.90 Intimal proliferation is concentric rather than eccentric, and the lesions are diffuse, involving both distal and proximal portions of the coronary tree. Calcification is uncommon, and the elastic lamina remains intact.

It is believed that the initiating event of CAV is subclinical endothelial cell injury in the coronary artery of the allograft. CAV leads to a cascade of immunologic processes involving cytokines, inflammatory mediators, complement activation, and leukocyte adhesion molecules. These changes produce inflammation leading ultimately to thrombosis, smooth muscle cell proliferation, and vessel constriction. The initial endothelial injury may be the result of ischemia–reperfusion damage or the host-vs.-graft immune response.91,92

The clinical diagnosis of CAV is difficult and complicated by allograft denervation resulting in silent myocardial ischemia. Ventricular arrhythmias, congestive HF, and sudden death are the initial common presentation of significant CAV. An annual coronary angiogram is performed routinely for CAV surveillance. Intravascular ultrasound (IVUS) is one of the best available methods and better equipped to provide important quantitative information regarding vessel wall morphology and the degree of intimal thickening.93 Noninvasive tests (eg, thallium scintigraphy and dobutamine stress echocardiography), have been used for additional screening for CAV.94 Other possible modalities include pulse-wave tissue Doppler imaging, electron beam computed tomography (CT), fast CT scanning, and MRI.

Treatment procedures such as stenting and angioplasty are inherently less effective in CAV-affected transplant patients because of the diffuse and distal nature of the disease, which results in a higher number of repeat procedures.95 Currently, the only definitive treatment for advanced CAV is retransplantation, which has risks for the patient and is associated with the scarcity of donor organs.95

Prophylactic management is of paramount importance. Prior to transplantation, the focus should be on preventing endothelial injury at brain death, reducing cold ischemia time, and improving myocardial preservation during storage and transportation. Post-transplantation care focuses on empirical risk factor modification such as dietary and pharmacologic reduction of serum cholesterol, cessation of smoking, and hypertension control. Several studies have demonstrated a decrease in CAV in patients treated with a calcium-channel blocker, and angiotensin-converting enzyme (ACE) and HMG-CoA reductase inhibitors.97,98

Newer immunosuppressive drugs, specifically the proliferation signal inhibitors (eg, everolimus and sirolimus), may be useful in reducing the incidence and severity of CAV and slowing disease progression.99,100

Renal Dysfunction

Cyclosporine nephrotoxicity after heart transplantation is well documented101 and lowering the cyclosporine dose may be helpful in slowing the progression of renal disease, especially with concomitant use of newer immunosuppressive regimens such as mycophenolate motefil and sirolimus. The 2005 ISHLT registry reported that only 60% of heart transplant recipients are free of severe renal dysfunction (>2.5 mg/dl) by Kaplan-Meier estimates at 9.5 years.

Hypertension

Moderate to severe systemic hypertension afflicts 50–90% of cardiac transplant recipients.87,102 Tacrolimus is associated with a lower incidence of hypertension compared with cyclosporine.103 Diuretics and β-blockers should be used cautiously, because of volume depletion/hypotension and blunting of the heart-rate response to exercise.

Malignancy

Chronic immunosuppression is associated with an increased incidence of malignancy (4–18%) and the most common malignancies are lymphoproliferative disorders and carcinoma of the skin etc. Treatment options in transplantation include a...
reduction in immunosuppression and high-dose acyclovir to attenuate EBV replication, in addition to conventional therapies for carcinoma such as chemotherapy, radiation therapy, and surgical resection.

Other Chronic Complications

Hyperlipidemia eventually develops in the majority of recipients and is managed with dietary restrictions, exercise, and lipid-lowering agents. Other complications may include osteoporosis, obesity, cachexia, and gastrointestinal complications.

Results of Heart Transplantation

The survival superiority of heart transplantation is evident in the medium- and high-risk patients with endstage HF when compared with the medical and device arms of the REMATCH trial. The 30-day operative mortality for cardiac transplantation ranges from 5% to 10% because of graft failure, multisystem organ failure, and infection, and the 1-year survival is up to 85%. During the first 6 months, there is a steep fall in survival and it decreases approximately 3.4% per year beyond 15 years post-transplantation. Infection, graft failure, and acute rejection are the leading causes of death during the first year. CAV and malignancy are the major causes of death thereafter. Questionnaires on QOL in cardiac transplant patients have demonstrated marked improvement and it approaches that of general population by 10 years after transplantation.

The Future

Development of reliable, noninvasive diagnostic studies to assess allograft rejection and the untoward effects of immunosuppression will allow more precise control of complications. Future improvements in organ preservation will permit a modest increase in the donor pool and better allocation of organs with respect to donor-recipient immunologic matching.

Further futuristic and miniaturized advanced assist devices to use as a destination therapy have the possibility to challenge the remarkable achievement of heart transplantation.

References

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