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Heart Transplantation for Advanced Heart Failure

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OUTLINE

Heart failure (HF) continues to be a leading cause of morbidity and mortality in the United States. Approximately 5.7 million Americans are currently living with HF; that number is expected to increase to more than 8 million by 2030. For the 915,000 new cases of HF diagnosed each year, 5-year mortality remains at approximately 50%.[1] The gross annual cost for managing HF is approximately $30.7 billion and is expected to reach $70 billion by 2030.[2] Strategies to avert these costs should focus on prevention considering that 75% of new HF cases are preceded by a history of hypertension.[3] Technologic advances continue to improve therapeutic options and outcomes for patients living with advanced HF (AHF). Ultimately, heart transplantation provides the best long-term outcomes for AHF patients.

IDENTIFYING ADVANCED HEART FAILURE

The cardiac intensivist must be adept at identifying, stabilizing, and treating the AHF patient. Depending on the practice environment and patient population, proficiency begins with:

1. Identifying AHF patients (Box 48.1)[4]
2. Determining which patients with AHF are potential heart transplant candidates
3. Managing critically ill heart transplant candidates, which includes:
   - Intensification of intravenous diuretics, vasodilators, and inotropes
   - Interpretation of hemodynamics to guide therapy

Keywords
heart transplantation
advanced heart failure

BOX 48.1 Diagnostic Criteria and Clinical Events Identifying Patients With Advanced Heart Failure

1. Diagnostic criteria
   a. Advanced NYHA functional class (NYHA class III-IV)
   b. Episodes of HF decompensation, characterized by either volume overload or reduced cardiac output
   c. Objective evidence of severe cardiac dysfunction shown by one of the following:
      i. LVEF <30%
      ii. Pseudo-normal or restrictive mitral inflow pattern
      iii. PCWP >16 mm Hg and/or RAP >12 mm Hg
      iv. Elevated BNP or NT-proBNP plasma levels in the absence of noncardiac causes
   d. Severe impairment of functional capacity shown by one of the following:
      i. Inability to exercise
      ii. Distance walked in 6 minutes ≤300 m
      iii. Peak oxygen consumption (VO_2) <12–14 mL•kg•min
   e. History of ≥1 HF hospitalizations in the past 6 months
   f. Presence of all of the previous features despite "attempts to optimize" therapy, unless these are poorly tolerated or contraindicated, and cardiac resynchronization therapy when indicated
2. Clinical events that suggest AHF
   a. Frequent (≥2) HF hospitalizations or ED visits in the past 12 months
   b. Progressive decline in renal function
   c. Cardiac cachexia
   d. Intolerance to ACE inhibitors because of hypotension or worsening renal function
   e. Intolerance to β-blockers because of hypotension or worsening HF
   f. Frequent systolic blood pressure <90 mm Hg
   g. Persistent dyspnea with dressing or bathing requiring rest
   h. Inability to walk 1 block on the level ground because of dyspnea or fatigue
   i. Escalation of diuretics to maintain euvolemia (furosemide dose >160 mg/day or use of metolazone)
   j. Progressive decline in serum sodium levels (<133 mEq/L)
   k. Frequent ICD shocks

ACE, Angiotensin-converting enzyme; *BNP,* B-type natriuretic peptide; ED, emergency department; ICD, implantable cardioverter-defibrillator; *LVEF,* left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; *NYHA,* New York Heart Association; *PWCP,* pulmonary capillary wedge pressure; *RAP,* right atrial pressure: VO_2, oxygen consumption.
Modified from Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the Management of heart failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013;128(16):e240-327; and Metra M, Ponikowski P, Dickstein K, et al. Advanced chronic heart failure: a position statement from the Study Group on Advanced Heart Failure of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail.* 2007;9(6-7):684–694.

   - Identification of optimal timing for mechanical circulatory support (MCS)
4. Proficiency in the immediate postoperative care following heart transplantation
5. Competency in the management of longer-term posttransplant complications that require cardiac intensive care unit (CICU) support;
   - Primary graft dysfunction
   - Acute and chronic rejection
   - Managing the denervated heart
   - Cardiac allograft vasculopathy
   - Complications of immunosuppression

EPIDEMIOLOGY

Of the almost 6 million Americans living with HF, approximately 200,000 patients have AHF or American College of Cardiology/American Heart Association (ACC/AHA) stage D heart failure.[5] Once an AHF or stage D patient is identified and determined to be high risk for rehospitalization, heart transplant or mechanical circulatory support candidacy should be determined. Critical to optimal patient outcomes is timely selection of the right intervention for the right patient. The limited supply of donor hearts warrants strict selection criteria, ensuring that those who are listed for heart transplantation are most likely to benefit. Box 48.2 outlines common elements used for evaluation of potential cardiac transplant candidates.

HEART TRANSPLANTATION INDICATIONS/CONTRAINDICATION

Box 48.3 outlines common indications for heart transplantation. It is important to have a solid background in these indications to ensure that necessary treatment is not delayed and that unnecessary testing and treatment is not performed. In addition, the intensivist must recognize that severe HF or suboptimally treated HF is an insufficient indication for heart transplantation. Many patients considered for advanced therapies may still have stage C HF and require only medical optimization.

Furthermore, the HF team must understand when heart transplantation is not an option or unlikely to be successful for a patient. Absolute and relative contraindications exist (Box 48.4); practice varies among transplant centers.

Recognizing risk factors and comorbidities helps determine the safety and appropriateness of transplantation for AHF patients and is critical to optimizing posttransplant outcomes. Members of every transplant center must work through their individual policies and determine what is an acceptable amount of risk while maintaining optimal outcomes.

Age

Age greater than 72 years is considered a relative contraindication to heart transplantation, based on work by Mancini and Lietz.[6] There are limited data on septuagenarians, but Goldstein et al.[7] reviewed 332 patients older than 70 years who underwent heart

BOX 48.2 Evaluation of Potential Cardiac Transplant Candidates

1. Detailed medical history and thorough physical examination
2. Laboratory evaluation
   - Complete blood count
   - Renal function tests
     - Blood urea nitrogen/creatinine
     - Creatinine clearance
     - Glomerular filtration rate
   - Liver function tests
     - Alkaline phosphatase
     - Bilirubin
     - Albumin
     - Transaminases
   - ABO blood type and antibody screen
   - Serologies for:
     - Hepatitis A, B, C
     - HIV (human immunodeficiency virus)
     - Cytomegalovirus
     - Epstein-Barr virus
     - Herpes simplex viruses I, II
     - *Toxoplasma gondii*
     - Syphilis
   - Skin test for tuberculosis with controls
   - Right heart catheterization
   - Left heart catheterization/coronary angiography, if indicated
   - Echocardiogram or other form of ventriculography, if indicated
   - Electrocardiogram
   - Chest radiograph
   - Carotid ultrasound, if indicated
   - Pulmonary function tests
   - Exercise testing with measured oxygen consumption, VO_2
   - Histocompatibility leukocyte antigen typing/panel reactive antibody
3. Psychosocial/financial consultation

BOX 48.3 Commonly Accepted Indications for Heart Transplantation

Cardiogenic shock with low probability of recovery
- Refractory volume overload and inability to wean ventilator
- Inability to wean temporary mechanical circulatory support
- Intraaortic balloon pump, ventricular assist device, ECMO
- Inability to wean continuous inotropic support

NYHA class IIIb or IV despite maximal medical and surgical therapy
- Including hypertrophic and restrictive cardiomyopathies
- Complex congenital heart disease not amenable to surgical or procedural intervention

Severe functional limitations secondary to underlying cardiac condition
- Peak oxygen consumption VO_2 ≤1214 mL/kg/min, or marked serial decline over time in the context of age appropriate controls
- 6-minute walk test <300 m

Ischemic heart disease with refractory CCS class III or IV angina pectoris despite optimal medical, surgical, and/or interventional therapy

Recurrent life-threatening ventricular arrhythmias despite optimal medical, electrophysiologic, and surgical therapy

Localized cardiac tumors with low likelihood of metastasis

CCS, Canadian Cardiovascular Society; *ECMO,* extracorporeal membrane oxygenation; *NYHA,* New York Heart Association.

transplantation and demonstrated median unadjusted survival of 8.5 years compared to 9.8 years in over 5800 sexagenarians. They concluded that select heart transplant candidates over the age of 70 years still derive great benefit from cardiac transplantation. It is generally accepted that heart transplant programs develop specific donor and recipient criteria in the context of their local organ availability and quality to ensure optimal outcomes and a high probability of transplantation for all patients listed.

Weight

There continues to be worse outcomes in patients at the extremes of the body mass index (BMI) spectrum, BMI less than 18.5 kg/m^2 and greater than 35 kg/m^2.[8,9] It is a class IIa recommendation[10] that patients achieve BMI less than 35 kg/m^2 before listing for heart transplantation. Additionally, there is a growing body of literature demonstrating safety and improved long-term outcomes in morbidly obese AHF patients who undergo bariatric surgery, some of whom are able to then go onto heart transplantation.

Diabetes Mellitus

Patients with diabetes mellitus (DM) who have no or minimal end-organ damage have excellent short- and intermediate-term outcomes with heart transplantation. Steroids will cause postprandial hyperglycemia, leading to worsened blood glucose control. Tacrolimus and cyclosporine will likely lead to end-organ damage, most commonly nephrotoxicity and/or neurotoxicity. The guidelines have adopted a class IIa recommendation stating a relative contraindication to heart transplantation in patients with DM and end-organ damage or persistent HbA1c levels greater than 7.5%.

Renal and Hepatic Impairment

AHF often leads to worsening renal and hepatic function. Cardiorenal syndrome and hepatic congestion can rapidly progress to irreversible stages. While no single test is an optimal predictor of recovery following heart transplantation, current guidelines recommend assessing renal function using estimated glomerular filtration rate (eGFR) or creatinine clearance. Evaluation often includes 24-hour proteinuria assessment, renal ultrasonography, and consultation with a nephrologist. The liver is more challenging than the kidney to predict degree of irreversible damage. Screening tools such as assessment of hepatic synthetic function (e.g., international normalized ratio [INR], platelets, albumin) are often misleading. Imaging of the liver, including abdominal ultrasound and abdominal computed tomography (CT), can often yield inconsistent results. The liver biopsy is being debated as a gold standard. Optimal liver biopsy specimens still have up to a 25% rate of discordance for fibrosis staging and an inherent risk of sampling bias.[11] Newer imaging techniques—such as ultrasound elastography/fibroscan, perfusion imaging with CT, and magnetic resonance elastography (MRE) may improve disease assessment. Transplantation candidates with marginal hepatic and renal function are not only at risk during the perioperative period but have higher long-term morbidity and mortality.

BOX 48.4 Commonly Accepted Contraindications for Heart Transplantation

Absolute Contraindications

Systemic illness with a life expectancy of <2 years despite HT, including

- Active or recent solid organ or blood malignancy within 5 years (e.g., leukemia, low-grade neoplasms of prostate with persistently elevated prostate-specific antigen)
- AIDS with frequent opportunistic infections
- Systemic lupus erythematosus, sarcoid, or amyloidosis that has multisystem involvement and is still active and not amenable to treatment
- Irreversible renal or hepatic dysfunction in patients considered for only HT
- Significant obstructive pulmonary disease (FEV_1 <1 L/min)
- Fixed pulmonary hypertension
- Pulmonary artery systolic pressure >60 mm Hg
- Mean transpulmonary gradient >15 mm Hg
- Pulmonary vascular resistance >6 Wood units

Relative Contraindications

- Age >72 years
- Any active infection (with exception of device-related infection in VAD recipients)
- Active peptic ulcer disease
- Severe diabetes mellitus with end-organ damage (neuropathy, nephropathy, or retinopathy)
- Severe peripheral vascular or cerebrovascular disease
  - Peripheral vascular disease not amenable to surgical or percutaneous therapy
  - Symptomatic carotid stenosis
  - Ankle brachial index <0.7
  - Uncorrected abdominal aortic aneurysm >6 cm
- Morbid obesity (body mass index >35 kg/m^2) or cachexia (body mass index <18 kg/m^2)
- Creatinine >2.5 mg/dL or creatinine clearance <25 mL/min[a]
- Bilirubin >2.5 mg/dL, serum transaminases >3×, INR >1.5 off warfarin
- Severe pulmonary dysfunction with FEV_1 <40% normal
- Recent pulmonary infarction within 6–8 weeks
- Difficult-to-control hypertension
- Irreversible neurologic or neuromuscular disorder
- Active mental illness or psychosocial instability
- Drug, tobacco, or alcohol abuse within 6 months
- Heparin-induced thrombocytopenia within 100 days

[a]May be suitable for HT if inotropic support and hemodynamic management produce a creatinine <2 mg/dL and creatinine clearance >50 mL/min. Transplantation may also be advisable as combined heart-kidney transplantation.

FEV_1, Forced expiratory volume in 1 second; *HT,* heart transplantation; *INR,* international normalized ratio; *VAD,* ventricular assist device.

Modified from Mancini D, Lietz K. Selection of cardiac transplantation candidates in 2010. *Circulation.* 2010;122:173–183.

Pulmonary Function

Severe chronic lung disease increases the risk of complications during the perioperative period and, independently, decreases the patient's functional capacity and chance for survival following transplantation. Patients with pulmonary dysfunction on immunosuppressive therapy demonstrate an increased incidence of pulmonary infection. Data are limited, but a single-center review of over 600 heart transplant patients demonstrated patients with FEV_1 (forced expiratory volume in one second)/FVC (forced vital capacity) ratio of 70% or less had significant prolongation of intubation and a significant reduction in 3-year survival compared to patients with FEV_1/FVC ratio greater than 70%. Similar outcomes were seen in patients with a diffusing capacity of the lungs for carbon monoxide (DLCO) less than 60%. Caution should be exercised when evaluating patients with abnormal pulmonary function tests for heart transplantation.

Pulmonary Hypertension

Left ventricular (LV) dysfunction is the most common cause of pulmonary hypertension worldwide. Pulmonary hypertension increases the risk for right ventricular failure during the perioperative period and significantly worsens mortality.[12] Patients under consideration for heart transplantation should undergo right heart catheterization (RHC). Several key parameters are determined at the time of RHC, including pulmonary vascular resistance (PVR), transpulmonary gradient (TPG), and the diastolic pulmonary gradient. Pulmonary artery (PA) systolic pressure greater than 50 mm Hg and a TPG greater than 15 mm Hg or a PVR greater than 3 Wood units is a class I recommendation to perform a vasodilator challenge. If these parameters can be corrected during initial hemodynamic measurement (e.g., with the administration of intravenous nitroprusside or an inotropic agent), it can safely be assumed that these abnormalities are secondary to the marked degree of cardiac dysfunction. Many AHF centers use indwelling PA catheters to allow for inpatient hemodynamic optimization. Select patients with severe cardiac dysfunction may require temporary MCS (tMCS) to fully unload the LV and allow for optimization of hemodynamics. This strategy may improve patient selection for durable MCS and, ultimately, patient outcomes. Durable MCS has been successful in lowering LV filling pressures over months, leading to negative remodeling. This strategy may provide marginal candidates the opportunity to become acceptable for heart transplantation. RHC should be routinely performed on patients based on risk factors and the clinical severity of disease in those who are being considered for heart transplantation. During episodes of decompensation or if patients are found to have unacceptably high PA pressures, admission to the CICU with PA catheter placement for medical optimization can be very helpful prior to transplantation. Young donor hearts with a naïve right ventricle (RV) have limited exposure to elevated pulmonary pressures and are at high risk for acute RV failure when transplanted into individuals with pulmonary hypertension. Patients with irreversible pulmonary hypertension may be considered for combined heart-lung transplantation.

Peripheral Vascular Disease and Cerebrovascular Disease

Severe symptomatic cerebrovascular or peripheral vascular disease can significantly hinder recovery and cardiac rehabilitation following heart transplantation. Registry data of over 1000 transplant patients with a history of symptomatic cerebrovascular disease

document an increased risk of stroke and functional decline following transplantation.[13] As part of the routine pretransplant evaluation, carotid Doppler ultrasound should be performed in patients with coronary artery disease or in patients older than 40 to 50 years. If significant carotid occlusive disease is identified, surgical correction should be strongly considered before transplantation. History and/or clinical signs or symptoms of peripheral vascular disease (PVD) should warrant appropriate screening and assessment, which may include lower extremity arterial Doppler evaluation and assessment of ankle-brachial indexes.

Infection

Transplanting in an individual with active infection is extremely high risk. The critical importance of immunosuppression immediately postoperatively leaves little room for error. It is routine to consult with an infectious disease specialist prior to transplantation if there are any active infectious concerns. Inpatient transplant candidates are particularly at risk for the development of a nosocomial infection. Meticulous attention to ongoing indications for indwelling lines or Foley catheters can help to avoid preventable infections. Practicing consistent sterile precautions while performing line maintenance can help prevent catheter-related infections. Using a very low threshold at the first sign of fever or leukocytosis to initiate a thorough investigation is recommended. At times, it is necessary to defer a patient's candidacy or downgrade a patient's listing status. An extensive infectious workup is performed on all potential transplant candidates. Finally, a thorough dental examination should be conducted before listing to identify patients with poor dentition and subclinical sources of infection. It is also important to recognize that patients who test positive for cytomegalovirus, *Toxoplasma gondii*, Epstein-Barr virus, hepatitis, human immunodeficiency virus (HIV), or prior tuberculosis (TB) infections can still be considered for heart transplantation. A transplant infectious disease physician can be instrumental in guiding therapy for this patient population, especially after the initiation of immunosuppression.

Malignancy

Transplantation significantly increases the incidence of malignancy, largely related to the effects of chronic immunosuppression. The prognosis, rate of progression, type of malignancy, response to treatment, and likelihood of widespread metastases must be thoroughly discussed and considered prior to proceeding with heart transplantation. Ongoing studies are needed to guide this decision process, especially for individuals with chemotherapy-induced cardiomyopathy.

Frailty

With an increasingly older population undergoing heart transplantation, accurate assessment of frailty is a growing area of interest. Frailty is a clinically recognized syndrome of decreased physiologic reserve that is often unmasked with only minor stressors. It is defined as a positive response to three or more of the following five components: weak grip strength, slowed walking speed, poor appetite, physical inactivity, and exhaustion. Frailty is an independent predictor of increased all-cause mortality in patients with AHF who are referred for heart transplantation.[14] The difficulty with evaluating frailty is a lack of standardization. Flint et al.[15] raise concern that not all frailty can be considered the same. They suggest that some frail patients may be appropriately treated with advanced therapy while others may not; therefore the current definition needs additional refinement and further study.

Psychosocial Issues

A comprehensive team evaluating all aspects of transplant candidacy, including psychosocial factors, is critical to optimizing patient outcomes and appropriate patient selection. A robust social support system is essential to the success of any patient undergoing heart transplantation. The vital nature of medication adherence, consistent follow-up, and early recognition of abnormal signs or symptoms are paramount to quality of life and long-term survival. The International Society for Heart and Lung Transplantation (ISHLT) guidelines provide a class IIa recommendation that "any patient for whom social supports are deemed insufficient to achieve compliant care in the outpatient setting may be regarded as having a relative contraindication to transplant."[16] Every heart transplant candidate should receive a careful and thorough evaluation by qualified professionals. Psychiatric conditions, including active substance abuse or prior substance abuse without clearly documented abstinence, may profoundly increase the risk of posttransplant complications. Tobacco use and alcohol abuse should be categorized with illicit drugs in estimating the scope of substance abuse. Marijuana has gained increasing attention as individual states have passed laws legalizing its use. The psychological stress of heart transplantation and its long-term sequela demand patient investment and commitment. Therefore it is important that psychosocial issues be addressed prior to heart transplantation.

Finances

The financial burden of heart transplantation varies significantly by region and insurance coverage. The estimated average 2014 billed charges associated with heart transplant in the United States[17] are as follows:

30 days pretransplant: $50,900
Procurement: $97,200
Hospital transplant admission: $771,500
Physician during transplant: $88,600
180 days posttransplant discharge: $198,400
Immunosuppressants and other medications: $35,600
Total: $ 1,242,200

These figures do not include the nonmedical costs associated with food, lodging, transportation to and from a transplant center, need for child care and lost wages for the patient and family member who may be required to leave work to function as a primary caretaker. While most insurers cover the expenses incurred in the transplant procedure itself, coverage varies dramatically for medications and long-term care. A comprehensive transplant team will have dedicated financial specialists who can assess the costs of future care based on an individual's insurance coverage. The goal of the financial team is to ensure that the

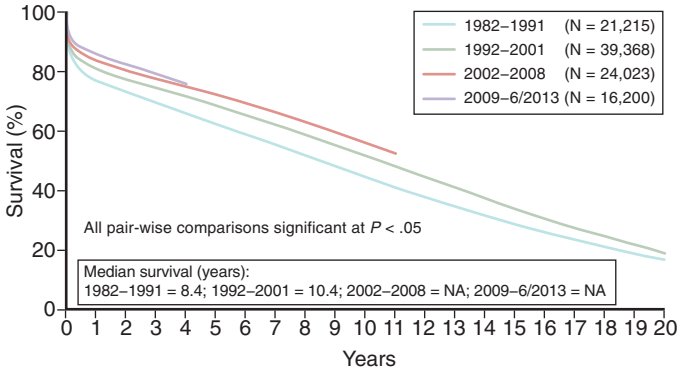

Fig. 48.1 Kaplan-Meier long-term survival for adult heart transplants performed between January 1982 and June 2013. Recipient survival improves with each successive 5 to 10 years; however, the major gains in survival are limited to the first 6 to 12 months, with the long-term attrition rate being unchanged. (Modified from Lund LH, Edwards LB, Kucheryavaya AY, et al. The registry of the International Society for Heart and Lung Transplantation: thirty-second official adult heart transplantation report—2015; focus theme: early graft failure. *J Heart Lung Transplant.* 2015;34:1244–1254.)

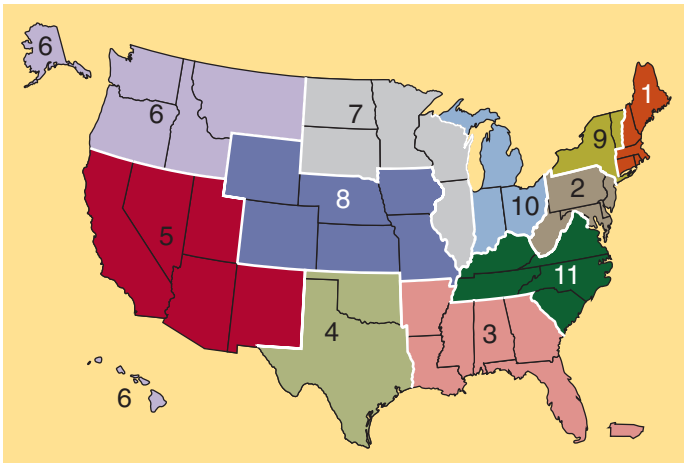

Fig. 48.2 Map of the 11 United Network for Organ Sharing regions in the United States. (Modified from Quader M, Wolfe L, Katlaps G, Kasirajan V. Donor heart utilization following cardiopulmonary arrest and resuscitation: influence of donor characteristics and wait times in transplant regions. *J Transplant.* 2014;2014:519401.)

family is prepared and capable of dealing with the financial burden of heart transplantation. Undergoing heart transplantation is physically, emotionally, and psychologically challenging. The burdensome financial strains add to the complexity and, ultimately, can lead to nonadherence to treatment plans and protocols, resulting in poor outcomes.

OVERVIEW OF HEART TRANSPLANTATION

Heart transplantation remains the most effective treatment for selected patients with AHF. Once transplanted, survival is significantly improved, as shown in Fig. 48.1.

Survival at 1, 10, and 20 years is nearly 90%, 50%, and 20%, respectively.[18] This is a dramatic improvement for AHF patients living with New York Heart Association (NYHA) class IV, stage D heart failure whose 5-year survival approaches zero.[4] Heart transplantation is limited primarily by a worsening supply-demand mismatch. As recently as 2012, nearly 2000 heart transplants were performed nationwide, yet over 3300 patients were on the waiting list with a 1- to 2-year survival of 50%.

Patients with AHF awaiting heart transplantation face not only the challenges of their disease process but the limitations of donor availability, regional differences in wait times (Fig. 48.2 and Table 48.1), and an increasingly complex donor allocation system. Since 2004, the annual number of cardiac transplants performed in the United States has slowly increased to approximately 2600 per year.

The median wait time for a patient listed as status 1A in Region 7 is approximately 90 days. The criteria required for patients to become listed as status 1A are presented in Table 48.2. It has been nearly a decade since the last revision of the heart allocation policy in the United States. Although during that time advances in medical therapy and drastic improvements in MCS options have helped to prolong survival, the status 1A

TABLE 48.1 Median Wait Time by Region for Status 1A Patients Awaiting Heart Transplantation and Mean Heart Transplant Volume Relative to a Region's Population

Region	Total Population	HTx Population	Mean HTx Volume/y	Median 1A Wait Time (d)
1	13,936,692	158,371	88	59.6
2	30,917,426	110,026	281	74.3
3	48,262,570	165,851	291	40.0
4	29,874,023	140,915	212	47.6
5	52,294,441	115,176	337	34.6
6	15,521,147	242,517	64	72.6
7	25,513,744	125,683	203	90.3
8	19,601,598	141,018	139	80.3
9	20,196,272	133,750	151	58.3
10	27,974,919	136,463	205	68.6
11	33,498,321	140,160	239	67.6

Modified from Quader M, Wolfe L, Katlaps G, Kasirajan V. Donor heart utilization following cardiopulmonary arrest and resuscitation: influence of donor characteristics and wait times in transplant regions. *J Transplant.* 2014;2014:519401.
HTx, Heart transplantation.

mortality rate remains unacceptably high.[19] An updated heart allocation policy with a six-tier system has been accepted and implemented in 2018.

The wait for heart transplantation is becoming longer for candidates due to several factors: a surge in the number of candidates, an increase in survival with the use of MCS as a bridge to transplant, and a plateau of acceptable donor hearts. The allocation of such a scarce resource warrants an investment in research and technology to help expand the donor pool.

In an effort to deliver the best outcomes with the highest quality of life to patients, intensivists must recognize the role

TABLE 48.2 United Network for Organ Sharing (UNOS) Heart Allocation Algorithm

Status Level	Category
Status 1A	Transplant candidate must be admitted to listing transplant center hospital and have at least one of the following devices or therapies in place I. Mechanical circulatory support for acute hemodynamic decompensation that includes at least one of the following: a. Candidates with implanted left and/or right ventricular assist device may be listed for 30 days under this criterion at any point after being implanted if treating physicians determine they are clinically stable—admittance to hospital not required. b. Total artificial heart c. Intraaortic balloon pump d. Extracorporeal membrane oxygenator (ECMO) II. Mechanical circulatory support with objective medical evidence of significant device-related complications III. Continuous mechanical ventilation IV. Continuous infusion of a single high-dose intravenous inotrope or multiple intravenous inotropes in addition to continuous hemodynamic monitoring of left ventricular filling pressures
Status 1B	Transplant candidate listed must have at least one of the following devices or therapies in place: I. Left and/or right ventricular assist device implanted II. Continuous infusion of intravenous inotropes
Status 2	A transplant candidate who does not meet the criteria for status 1A or 1B
Status 7	A transplant candidate who is considered temporarily unsuitable to receive a heart transplant

Modified from Kilic A, Emani S, Sai-Sudhakar C, Higgins R, Whitson B. Donor selection in heart transplantation. *J Thorac Dis.* 2014;6(8):1097–1104.

BOX 48.5 Indications of Intolerance of Current Medical Management

Worsening Cardiovascular Symptoms
- Easy fatigability
- Increasing frequency and severity of angina
- Exertional dyspnea/shortness of breath at rest
- Orthopnea/paroxysmal nocturnal dyspnea
- Dysrhythmia (tachycardia, palpitations)

Worsening Cardiovascular Physical Signs
- Hypotension/narrow pulse pressure
- Resting tachycardia/frequent ventricular ectopy/atrial fibrillation
- Elevated jugular venous pressure
- Prominent S_3/S_4
- Loud murmur of mitral/tricuspid regurgitation
- Hepatomegaly/ascites/hepatojugular reflux
- Edema/anasarca
- Diminished peripheral perfusion (cyanosis/delayed capillary refill)

Worsening Objective Measures of Cardiac Performance
- Diminished renal perfusion (prerenal azotemia/rising serum creatinine)
- Hepatic congestion (elevated liver function tests)
- Decreased end-organ perfusion (metabolic acidosis/elevated serum lactate)
- Deteriorating left ventricular function by echocardiogram
- Decreased left ventricular ejection fraction by radionuclide ventriculography
- Worsened cardiomegaly/pulmonary edema on chest radiograph
- Diminished maximal oxygen consumption VO_2 on exercise testing
- Abnormal parameters on right heart catheterization
- Elevated central venous pressure
- Worsening pulmonary arterial hypertension/pulmonary vascular resistance
- Declining cardiac output/cardiac index
- Increasing arteriovenous oxygen difference ($A - VO_2$)

of the multidisciplinary cardiovascular care team (Fig. 48.3), which includes cardiothoracic surgeons, mechanical circulatory support teams, interventional/structural cardiologists, critical care teams, AHF cardiologists, and supportive/palliative care physicians. Such a collaborative approach is fundamental for optimal patient care.[20] Several randomized controlled trials have demonstrated that multidisciplinary team-based care for patients with AHF can reduce mortality by 25% to 46%, HF hospitalization by 25%, and all-cause hospitalizations by 20% to 30%.[21] Additional studies have confirmed that the implementation of team-based care for AHF decreases length of stay and improves quality of life.[22,23]

PRETRANSPLANT PATIENT CARE

Pretransplant patient management starts with early recognition of patients with AHF. There are several levels of care that a patient with AHF awaiting heart transplantation may require; the physician must determine which will be sufficient. Many patients can be managed in the outpatient setting and remain listed as status 2. Frequent outpatient visits and assessment of adequate metabolic, cellular, and nutritional health are critical in preventing irreversible end-organ damage. The common symptoms, physical signs, and objective measures of cardiopulmonary status are listed in Box 48.5.

There is no single parameter that identifies an individual who would benefit from heart transplantation. LV ejection fraction (LVEF) was previously thought to be the primary indicator of worsening prognosis and survival, but we now know that LVEF fails to consistently predict outcomes and, alone, is an inadequate indication for heart transplantation. Nearly 50% of HF patients have HF with preserved ejection fraction (HFpEF). The field of AHF must find better ways of predicting outcomes and obtaining objective data points that can assist in predicting outcomes for this patient population. Two diagnostic tests, RHC and cardiopulmonary exercise testing (CPET), provide reliable, objective data that are helpful in evaluating patients with AHF.

RHC has a class I recommendation for all adult candidates in preparation for listing for heart transplantation. In addition, an RHC should periodically be performed on candidates awaiting heart transplantation at a frequency that is personalized to each individual situation. With the development of ambulatory PA pressure monitoring systems, such as the CardioMEMS[24] (Abbott) device, future guidelines may need to consider alternatives to recurrent invasive procedures.

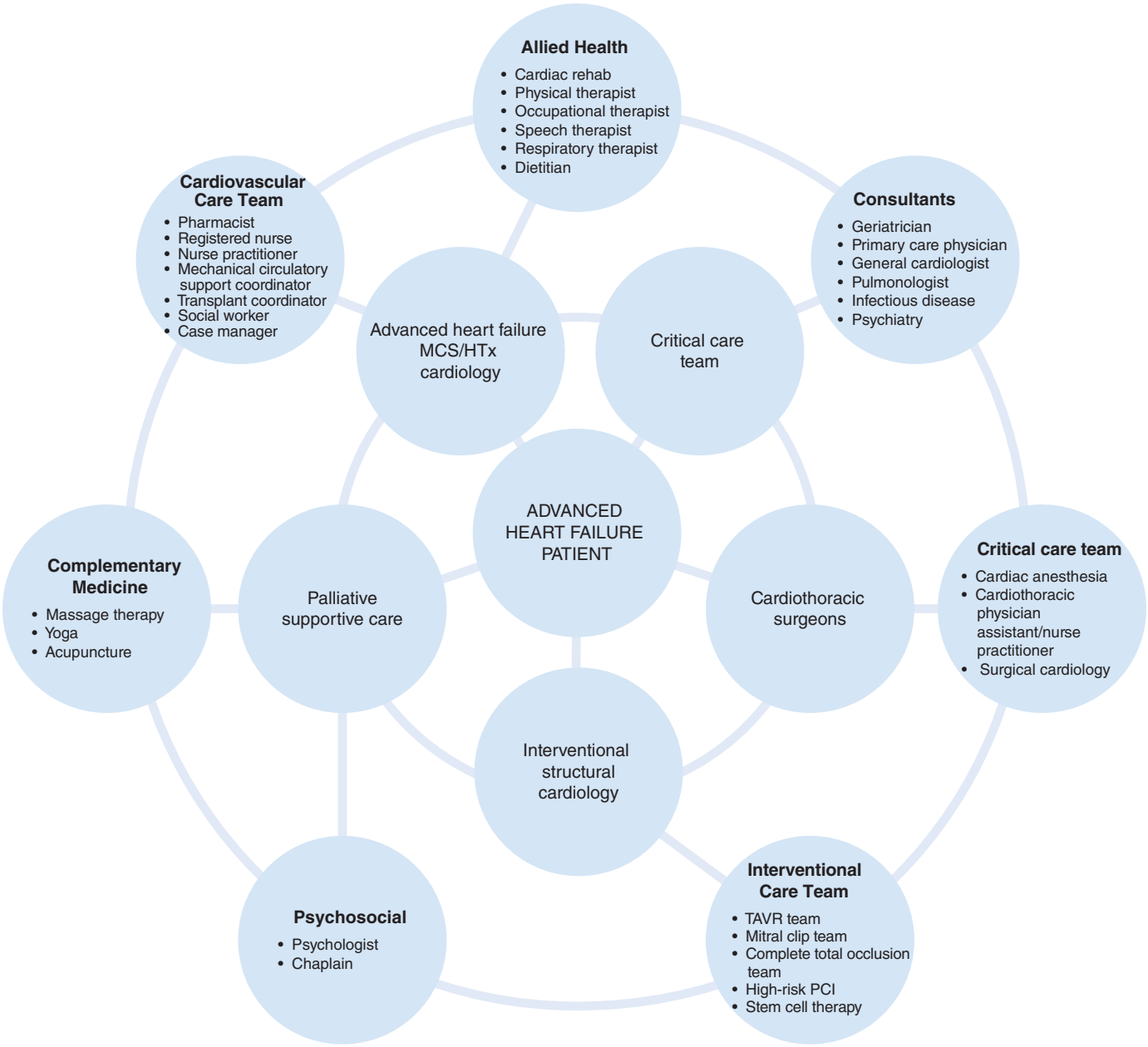

Fig. 48.3 An integrated model of team-based care for advanced heart failure patients incorporating multidisciplines while maintaining the patient at the center of the care plan. *HTx,* Heart transplant; *MCS,* mechanical circulatory support; *PCI,* percutaneous coronary intervention. (Modified from Fendler TJ, Swetz KM, Allen LA. Team-based palliative and end-of-life care for heart failure. *Heart Fail Clin.* 2015;11(3):479–498.)

Recent trials have built upon the foundational work of Mancini and colleagues on the use of CPET as a tool for predicting outcomes in AHF patients.[25] They found that a peak VO_2 of less than 14 mL/kg per minute can be used to predict a 1-year mortality benefit with heart transplantation in patients with AHF. CPET has been integrated into recent scientific statements.[26–28] Multiple studies have demonstrated the utility of measuring exercise capacity and oxygen consumption to assist in determining the degree of cardiac dysfunction and prognosis.[29] As our knowledge and understanding of the pathophysiology of AHF have matured, we have developed a better understanding of why the functional reserve capacity in AHF patients is limited. Exercise capacity in AHF patients is impaired by abnormal O_2 uptake in the lungs, progressive anemia limiting O_2 transport to skeletal muscle, reduced cardiac output in the setting of chronotropic and inotropic incompetence, and impaired vasoreactivity. The careful measurement of both ventilatory and peripheral O_2 uptake patterns can provide both prognostic value and quantification of disease severity.[30]

The use of HF prognosis scores such as the Heart Failure Survival Score (HFSS) or the Seattle Heart Failure Model (SHFM) may be used to predict morbidity and mortality in ambulatory AHF patients and assist in discriminating patients who should be listed for transplantation.[31] Predicted patient survival of less

BOX 48.6 Acute Precipitants of Acute Decompensated Heart Failure

Dietary indiscretion: high salt intake
Pulmonary infections
Medication changes or nonadherence
Arrhythmias and antidysrhythmic medications
Anemia
Thyroid dysfunction

Data from Tsuyuki RT, McKelvie RS, Arnold JMO, et al. Acute precipitants of congestive heart failure exacerbations. *Arch Intern Med.* 2001;161.19:2337–2342.

than 80% at 1 year by the SHFM or in the medium- to high-risk range by the HFSS is considered a reasonable threshold for listing for cardiac transplantation. Risk calculators such as the SHFM[32] were developed for predicting events in outpatient cohorts, which limits their applicability to hospitalized AHF patients. While survival scores can be helpful in prognostication, listing patients for heart transplantation based only on survival risk scores is a class III recommendation and should be avoided.

Acute Precipitants of Heart Failure Exacerbations

As HF progresses toward the advanced stages, patients become increasingly more susceptible to decompensation. Events that may have been well tolerated early in the disease process become increasingly difficult for patients to manage without inpatient care. Box 48.6 lists acute precipitants of acute decompensated HF, which is also discussed in greater detail in Chapter 18.[33] Many of the precipitating conditions are easily reversible but should lead the clinician to quickly review optimization of guideline-directed medical therapy (GDMT), indications for implantable cardioverter defibrillators (ICDs), and cardiac resynchronization therapy (CRT), and ensure that there is no reversible structural abnormality contributing to the patient's condition. These strategies should have been used earlier in the course of the disease, but in a recent review[34] of over 1000 consecutive patients listed for heart transplant, only 51% of the patients had an ICD in place at the time of being listed. Patients who suffer decompensation due to arrhythmia may benefit from an electrophysiology evaluation. Options include ablative procedures, optimization of antidysrhythmic regimens, and, in some cases, surgical sympathectomy to treat potentially lethal ventricular arrhythmias. If loss of sinus rhythm is thought to have been a precipitant of the decompensation, a robust attempt should be made to establish and maintain sinus rhythm. Based on the 2013 ACC/AHA guidelines, amiodarone and dofetilide are the preferred antidysrhythmic drugs largely based on their neutral effect on mortality in the HF population.

Guideline-Directed Medical Therapy

It is relatively common for patients presenting to the hospital with decompensated HF to have their β-blocker withheld. Only when there is cardiogenic shock, tissue hypoperfusion, and/or the initiation of inotropic therapy should β-blockers be withheld. Patients taking β-blockers who develop decompensated HF should be maintained on their medication if at all possible. Hemodynamic goals may necessitate dose adjustment; however, every effort should be made to continue β-blocker therapy.

The deescalation of GDMT is a disservice to HF patients in terms of mortality, but is clinically indicated on occasion. Renal dysfunction, symptomatic hypotension, and electrolyte disturbances are the most frequent reasons for discontinuing angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), sacubutril/valsartan (an angiotensin receptor neprilysin inhibitor [ARNI]), and aldosterone antagonists. Patients who can no longer tolerate GDMT should be recognized as individuals in need of advanced therapy. Patients with renal dysfunction warrant special attention with frequent laboratory assessment when initiating or adjusting dosages of the above medications. In general, systolic blood pressure less than 80 mmHg, serum creatinine greater than 2.5 mg/dL in men and greater than 2.0 mg/dL in women, or a serum potassium level greater than 5.0 mmol/L should give pause to clinicians when considering initiation of an ACE inhibitor, ARB, ARNI, or aldosterone antagonist. Although patients with serum sodium less than 132 mM/L are at increased risk for symptomatic hypotension with ACE inhibitors, they derive the greatest benefit. Hydralazine and isosorbide dinitrate have a unique class I recommendation for use in African Americans with NYHA class III to IV HF with reduced ejection fraction (HFrEF) but are still a class IIa recommendation for any symptomatic patient with HFrEF who cannot take ACE inhibitors, ARBs, or ARNIs.

Other Common Heart Failure Drugs

Digoxin remains a controversial drug with a class IIa recommendation for patients with HFrEF to reduce hospitalizations for HF. Guidelines recommend 0.125 to 0.25 mg daily, with even lower doses for patients greater than 70 years old, impaired renal function, or low lean body mass. Serum levels between 0.5 and 0.9 ng/mL are suggested, as higher drug levels are unlikely to provide additional benefit and are more likely to lead to toxicity, especially when the level is greater than 2 ng/mL. Increased risk for digoxin toxicity occurs with concomitant amiodarone use and close monitoring should be done in patients with labile renal function. In addition, calcium channel blockers are not recommended for patients with HFrEF and should be avoided, with the exception of amlodipine for the treatment of hypertension or angina. Last, anticoagulants are not recommended in patients with chronic HFrEF without atrial fibrillation, a prior thromboembolic event, or an embolic event from a presumed cardiac source.

Medical Therapy in Advanced Heart Failure

The natural disease course in AHF leads to progressive functional decline with many of the clinical signs and symptoms listed in Box 48.5. One of the many challenges in treating AHF patients is understanding that a successful strategy to treat one patient does not always translate into a successful strategy for the next patient. As previously mentioned, a low threshold for hospitalization, intensification of therapy, and avoidance of end-organ damage are important in slowing the disease progression.

As AHF progresses, therapy is often escalated from intravenous diuretics to intravenous inotropic agents. Technological

advances have made the role of tMCS increasingly important. It is common for patients who are failing intravenous inotropic agents to undergo placement of an intraaortic balloon pump (IABP) or tMCS as a temporizing measure to determine if a patient can be successfully bridged to a more long-term solution (heart transplantation or durable MCS). Again, this advanced stage of HF is frequently characterized by the deescalation of therapy that initially was well tolerated. Several common clinical problems arise during this stage, which is discussed in greater detail here.

Many patients present acutely with decompensated HF and in critical condition, requiring admission to a CICU. Recognizing the level of required care to gain control of and stabilize progression of the disease is a critical skill set that can determine life or death for this patient population. If inappropriately triaged, patients are at risk of suffering compromised end-organ function, which ultimately worsens posttransplant morbidity and mortality. Data from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial[35] played a significant role in the decreased use of invasive hemodynamic monitoring with PA catheters. The guidelines provide a class III recommendation for the *routine use* of invasive hemodynamic monitoring in normotensive patients with acute decompensated HF. However, invasive hemodynamic monitoring to guide therapy in patients who have respiratory distress or clinical evidence of impaired perfusion is still a class I recommendation. The role for invasive hemodynamic monitoring in AHF patients is a critical step in determining the reversibility of elevated pulmonary pressures and increased pulmonary vascular resistance. While PA catheters are not therapeutic, the data they provide can help guide therapy and prognosis and possibly improve outcomes before and after heart transplantation.

Relief of Congestion

Symptomatic relief for patients with AHF can often be achieved using loop diuretics in high doses or in continuous infusions. Both strategies proved comparable in the Diuretic Optimization Strategies Evaluation (DOSE) trial, albeit at low infusion doses.[36] As AHF progresses and diuretic resistance develops, effective diuresis often necessitates the combination of loop diuretics and metolazone or intravenous thiazides. When creatinine rises and diuretic resistance develops, the intensivist must recognize worsening cardiorenal syndrome. Cardiorenal syndrome may require support from inotropic infusions or the use of tMCS to help relieve congestion and improve renal function. In some refractory cases, the administration of nesiritide has been successful at promoting diuresis. Nesiritide gained popularity following the Vasodilation in the Management of Acute CHF (VMAC) trial,[37] but subsequently lost favor when the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure Trial (ASCEND-HF) trial[38] published its findings. Ultrafiltration (UF) has been studied in both the Ultrafiltration versus IV Diuretics for Patients Hospitalized for Acute Decompensated CHF (UNLOAD) trial[39] and the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) trial,[40] with mixed results. Ongoing enrollment in the Aquapheresis Versus Intravenous Diuretics and Hospitalization for Heart Failure (AVOID-HF) trial may help to determine if early use of UF will reduce heart failure events and has a role in pretransplant patient care.

Pleural effusions and ascites are common signs of congestion. Patients can experience significant relief following thoracentesis or paracentesis. It is imperative to understand that restoration of normal volume status markedly enhances the response to vasodilators. Decongesting a patient may afford the opportunity to reinitiate GDMT, but previously ineffective doses may result in effective or even excessive vasodilation. Although it is common for the initiation of GDMT to lead to a rise in creatinine, diuretics should not be withheld. Many effectively treated patients will experience an increase in creatinine and blood urea nitrogen, often by as much as 50%, which is acceptable. One strategy to deal with worsening renal function is to slow the rate of diuresis if the patient is no longer volume overloaded and to avoid excessive vasodilation. If the patient is in a low-output state, cardiac output must be optimized before effective diuresis can be achieved without compromising end-organ function.

Role for Intravenous Inotropic and Vasodilator Therapy

Most AHF patients awaiting heart transplantation will require inotropic support to be successfully bridged to MCS or heart transplantation. The guiding principal when using inotropes is to apply as low a dose as possible for the shortest necessary duration to achieve the clinical goal. Some patients will require the placement of long-term IV access and the initiation of home inotrope infusion. Most cardiac intensivists are most comfortable using dobutamine and milrinone for inotropic support. In patients with hypotension, dopamine—and occasionally epinephrine—can provide blood pressure and inotropic support. Data from De Backer et al.[41] compared dopamine with levophed in over 1600 patients presenting with shock and noted no significant difference in mortality; however, 24% of patients on dopamine compared to 12% of patients on levophed experienced arrhythmias ($P = .01$). Furthermore, a subgroup analysis found that in 280 cardiogenic shock patients, 28-day mortality was significantly higher in those treated with dopamine compared to those treated with levophed ($P = .03$). There are situations in which isoproterenol may also be considered for very-short-term support.

Understanding the physiology and side-effect profiles of these medications allows precision therapy for AHF patients. In general, the adverse effects of these medications are duration dependent and dose dependent; combining agents at lower doses may help avoid adverse events. Patient dependence upon continuous IV inotropic support is a poor prognostic indicator and signals the very final stages of AHF. The United Network for Organ Sharing (UNOS) status listing acknowledges the increased morbidity and mortality associated with continuous IV inotropes; thus these patients are given higher priority on the waiting list. Caution must be exerted when transitioning off inotropic support. Patients frequently become overly sensitive to afterload reduction in the setting of intravascular depletion or while titrating down inotropic support. Therefore, special attention should be given to assessing the patient's volume status and tolerance of vasodilators. The

role for PA catheter-guided management of hemodynamics with special attention to the SVR can help avoid this clinical scenario. Renal vascular vasodilation and renal vascular congestion can both lead to a rise in serum creatinine. Anticipating and differentiating between these events can help prevent patient mismanagement. "Start low and go slow" is an appropriate strategy when it comes to oral vasodilator dosing prior to discontinuation of inotropic therapy. In the clinical scenario in which inotropic weaning is unsuccessful, a plan for palliative care, bridge to MCS, or bridge to transplantation should be put in place. When a patient is discharged on inotropic support that is not palliative, ICD placement should be considered given the increased risk for arrhythmia-related, sudden cardiac death.

Not all AHF patients will require inotropic support. PA catheter placement may provide hemodynamic data that suggest significantly elevated SVR. In this situation, the use of intravenous vasodilators, such as nitroprusside or nitroglycerin, can offer important clinical benefit. Patients with ischemic cardiomyopathy or pulmonary hypertension complicated by severe right heart failure may respond well to intravenous nitroglycerin. Nitroprusside has also been used in this setting but caution must be exercised in patients with renal failure, as they are at higher risk for the development of thiocyanate toxicity.

Mechanical Circulatory Support

MCS continues to play an increasing role in the treatment of AHF. In the past 9 years, over 15,000 patients have been implanted in the United States, and the current rate of implantation exceeds 2000 patients per year.[42] Approximately 30% of those recipients were listed for heart transplantation at the time of implant and an additional 23% were implanted with the plan of bridge-to-transplant (BTT) strategy. Technology is advancing rapidly in this field and, while 1-year survival now approaches 80%, it is still well below the 90% survival at 1 year for heart transplantation. Durable and temporary devices, including extracorporeal membrane oxygenators (ECMOs), will likely play an increasing role in improving survival to heart transplantation. MCS is discussed in much greater detail in Chapters 49 and 50, including both percutaneously and surgically implanted options.

Immediate Pretransplant Considerations

In 1984, the United States created the Organ Procurement and Transplant Network (OPTN) to help develop a system that would guide organ allocation. The UNOS is the only nonprofit organization that has ever run the OPTN and has been managing it since the initial contract was awarded in 1986. The UNOS has helped to develop an organ-sharing system in which donor hearts are allocated based on degree of illness in the recipient, blood type compatibility, size disparity, and length of time that the candidate has been actively waiting for transplantation. The algorithm for listing patients has evolved over the years: in 1988 there were two tiers; in 1989, there were three tiers; and in 2006, the system was modified for broader organ sharing. The current heart allocation system is based on 3 tiers of medical urgency: status 1A, status 1B, and status 2. Status 1A is given the highest priority on the waiting list; status 2 represents the more stable candidate, generally awaiting transplant at home. The field of heart transplantation has recognized the need to decrease time on the waiting list and related mortality. In 2015, a new system with six tiers was proposed and has undergone public comment and expert refinement.[43] As of 2017, the OPTN and UNOS approved the revised adult allocation system with ongoing modification. As of 2018, the new system better incorporates the advances of MCS and its increasing role in helping to successfully bridge candidates to heart transplantation.

ABO Blood Type

Organ donors and transplant recipients are paired based on ABO blood type matching. There are 3 categories of ABO matching: ABO identical, ABO compatible, and ABO incompatible.[44] ABO blood type plays an important role in expected wait times for status 1A patients. This should be considered when listing critically ill patients who may need MCS to successfully bridge them to transplant.

Body Weight

Current guidelines from the ISHLT provide a class I recommendation that adult heart donors' body weight be within 30% of the recipients. Further, they recommend that a female-to-male donation be within 20%. The guidelines state that a male donor of average weight (70 kg) can be safely used for any recipient regardless of weight.[45]

Heart Transplantation Morbidity and Mortality

The driving forces of morbidity and mortality in heart transplantation are highly related to the time from transplantation. Understanding this temporal relationship may help guide the initial work-up and treatment for heart transplant patients who present with nonspecific symptoms, especially in the CICU (Fig. 48.4).

For cardiac intensivists taking care of heart transplant patients, it is important to recognize that most infections and rejection episodes are treatable. Furthermore, advances in both durable and tMCS are expanding rescue options and the candidate pool.

POSTTRANSPLANT PATIENT CARE

Hemodynamics

The physiology of the transplanted heart is far different than that of most other cardiac patients. In the immediate postoperative period, the transplanted heart usually requires higher-than-normal filling pressures. PA catheters play a critical role in targeting optimal filling pressures for every posttransplant patient. In general, optimal right-sided preload is usually a right atrial pressure between 8 and 15 mm Hg and optimal left-sided preload is a pulmonary capillary wedge of 15 to 20 mm Hg. The elevated filling pressures are thought to be driven by the dramatic decrease in ventricular compliance and diastolic dysfunction after transplantation. Given the degree of diastolic dysfunction and limited stroke volume following heart transplantation, a heart rate of 100 to 120 beats/min is targeted to maintain optimal cardiac output.

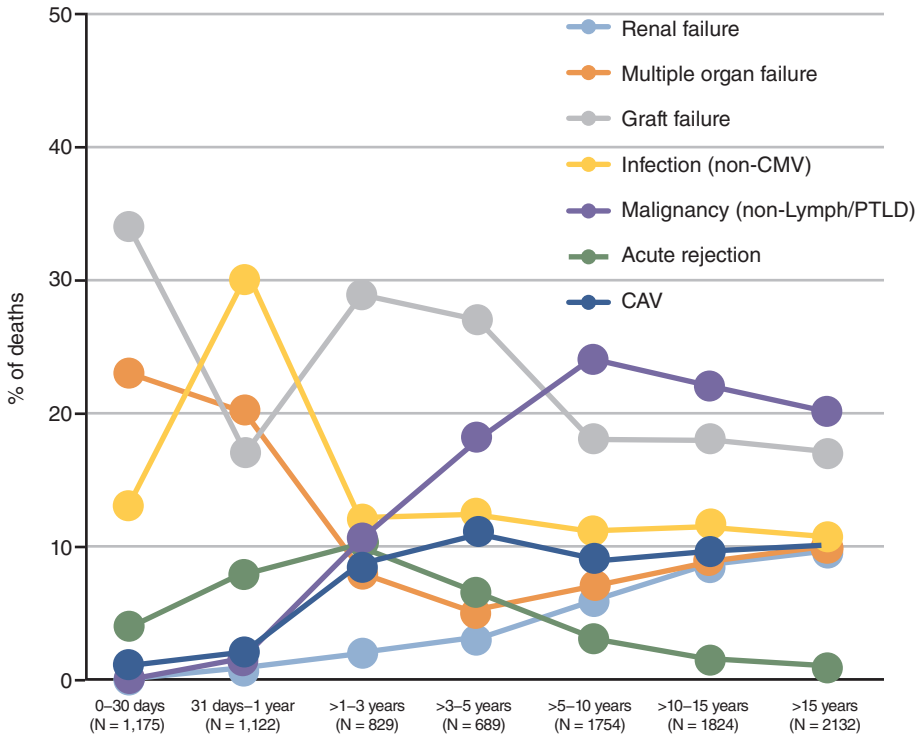

Fig. 48.4 The seven most common causes of death in post–heart transplant patients. Time from transplant on the *x*-axis demonstrates significant variation in the most common etiology leading to death. *CAV*, Cardiac allograft vasculopathy; *CMV*, cytomegalovirus; *PTLD*, posttransplantation lymphoproliferative disorder. (Modified from Lund LH, Edwards LB, Kucheryavaya AY, et al. The registry of the International Society for Heart and Lung Transplantation: thirty-second official adult heart transplantation report—2015; focus theme: early graft failure. *J Heart Lung Transplant*. 2015;34:1244–1254.)

Inotropic Support

Approaches to postoperative inotropic support in heart transplantation patients vary by center. Unfortunately, there are few data to guide protocols. Isoproterenol use is uncommon in the CICU, but it is used in doses of 0.25 to 5.00 μg/min for the newly admitted postoperative heart transplant patient. Some institutions argue that the potential lusitropic effect of isoproteronol enhances diastolic relaxation. Typically, heart transplant recipients will require some degree of inotropic support: dobutamine (3.0 to 10.0 μg/kg per minute), milrinone (0.37 to 0.75 μg/kg per minute), dopamine (1.0 to 5.0 μg/kg per minute), and/or epinephrine (1.0 to 5.0 μg/min) are commonly used. The β-adrenergic receptors of the denervated heart are extremely sensitive to β-adrenergic agonists. The duration of inotropic support is often affected by the donor/recipient age, ischemic time, and effectiveness of cardioplegia. Many transplant programs have implemented critical care protocols for inotropic weaning that typically occurs over 2 to 5 days.

Ventilation

In uncomplicated heart transplantation, the critical care team is often able to rapidly wean sedation, assess the neurologic status, and provide the patient a spontaneous breathing trial prior to extubation within the first 6 to 12 hours postoperatively. Individuals with severe RV dysfunction, volume overload, marginal pulmonary function, or high inhaled nitric oxide requirements will typically be weaned more slowly prior to attempted extubation. Prolonged intubations increase the risk for ventilator-associated pneumonia, especially in the posttransplant population who are significantly immunosuppressed.

IMMEDIATE POSTOPERATIVE COMPLICATIONS

The first 72 hours following heart transplantation is critical for both the short- and long-term prognosis of the patient. Major complications are discussed later. Vital to the success of the intensive care team is the ability to anticipate problems before they reach an irreversible point and respond with urgent intervention.

Cardiac Denervation

One major difference in heart transplant recipients is their arrival to the CICU with a denervated heart. The cardiac physiology in a denervated heart is unique and deserves special attention.[46] Normal cardiac physiology involves both sympathetic and parasympathetic innervation by the autonomic nervous system. During heart transplantation, there is complete transection of neural axons to the heart, resulting in loss of cardiac norepinephrine reserves. Afferent denervation impairs the response to changes in cardiac filling pressures. Sympathetic and parasympathetic regulation is

diminished by efferent denervation, resulting in an elevated resting heart rate and decreased inotropic and chronotropic responses to exercise. Normal sinoatrial (SA) node activity is often impaired after heart transplantation. Initially, many patients suffer from relative sinus bradycardia. This is often a result of trauma to the SA node following surgery, prolonged ischemic time, or amiodarone use in the recipient prior to heart transplantation. This is often treated with temporary cardiac pacing through surgically placed epicardial pacing wires. Terbutaline has been used with mixed results to temporarily increase resting heart rates following weaning from inotropes. Most patients are able to discontinue terbutaline within the first month after transplant; less than 5% of patients will require pacemaker implantation.

Arrhythmias

Sinus tachycardia is the most commonly encountered arrhythmia and is considered the normal physiologic response to denervation. Postoperative atrial arrhythmias (including atrial tachycardia, atrial flutter, and atrial fibrillation) occurred at rates up to 50% in older series.[47] Surgical technique may have reduced the occurrence rate, as the bicaval approach has increasingly replaced the biatrial anastomosis. Arrhythmias may be triggered by postoperative inflammation originating from suture lines or from high-dose inotropic support in the immediate postoperative period. The denervated heart is especially sensitive to AV nodal blocking agents. Attempts at reducing inotropes should be the initial intervention followed by the cautious consideration of calcium channel blockers and, less preferably, β-blockers. If there is concern for LV dysfunction, amiodarone should be considered.

Digoxin is unlikely to be effective in cardiac transplant patients given that its primary mechanism of action is through its effect on vagal tone. Extreme caution must be applied if considering adenosine, as it can result in prolonged ventricular asystole. If adenosine is considered in a heart transplant patient, we recommend no more than 3 mg via a peripheral IV or 1.5 mg via a central IV. Additionally, it should be kept in mind that rate controlling agents such as verapamil, diltiazem, and amiodarone can significantly increase immunosuppression drug levels.

Vasoplegia Syndrome

Vasoplegia syndrome (VS) is rare but can be lethal following heart transplantation. It consists of severe refractory hypotension, metabolic acidosis, and low systemic vascular resistance.[48] VS is seen following cardiac surgery using cardiopulmonary bypass and is not unique to heart transplantation. Risk factors include preoperative intravenous heparin, ACE inhibitors, and calcium channel blockers. The incidence of VS may also be increased in individuals who are bridged to transplant with MCS. The pathophysiology is thought to be related to the upregulation of several vasodilatory mechanisms, including circulating interleukin-1,[49] endothelial injury,[50] and dysregulation of nitric oxide synthesis. In addition, an association between vasodilatory shock and vasopressin deficiency was described by Argenziano et al.[51] Treatment approaches include hemodynamic support with vasopressors.[52] Norepinephrine, vasopressin, and pure α-adrenergic agonists, such as phenylephrine, have typically been able to restore mean arterial blood pressure. When refractory hypotension is present despite optimal vasopressor support, methylene blue has been used to treat VS following heart transplantation.[53] Methylene blue can be given as a single infusion over 20 minutes, typically 2 mg/kg as described by Leyh et al.[54] Following infusion of methylene blue, patients may develop greenish discoloration of the urine and, occasionally, the skin. Pulse oximetry is unreliable because of light emission interference by methylene blue. A 25% mortality has been seen when methylene blue is used in individuals with severe renal insufficiency and G6PD deficiency.

Hyperacute Rejection

Assessing compatibility for both ABO blood group and major histocompatibility antigens prior to transplantation has dramatically decreased the incidence of hyperacute rejection. Hyperacute rejection occurs when circulating preformed antibodies to the donor heart are present, resulting in graft failure within minutes to hours of transplantation. Immediate MCS is typically required in the form of ECMO. Plasmapheresis and aggressive immunosuppression focusing on eliminating or removing the preformed antibodies provides the best chance of survival for these individuals. Antithymocyte globulin (ATG), intravenous immunoglobulin (IVIG), and complement inhibitors such as eculizumab have been used to treat this complication. For patients in cardiogenic shock, ECMO support may be indicated while antirejection therapy is being administered.

Right Ventricular Failure

RV failure is another common complication in the immediate postoperative period. Several factors contribute to the likelihood of RV failure. In most younger donor hearts, the RV is naïve to elevated PA pressures and is, therefore, susceptible to acute RV failure at time of implantation into a recipient with pulmonary hypertension. This principal was demonstrated in animal models in the 1950s by Guyton et al.[55] Several early posttransplant deaths in the 1960s were attributed to acute RV failure in patients with known pulmonary hypertension. In the 1970s, the risk of death from acute RV failure following heart transplantation was reported by Griepp et al.[56] See Box 48.7 for goals in the treatment of acute RV failure adapted from Stobierska-Dzierzek et al.[57]

RV failure is characterized by progressive congestive symptoms with impaired RV filling and/or reduced cardiac output. Increased RV afterload or preload leads to ventricular dilatation

BOX 48.7 Goals in the Treatment of Acute Right Ventricular Failure

1. Preserving coronary perfusion through maintenance of systemic blood pressure.
2. Optimizing right ventricular preload.
3. Reducing right ventricular afterload by decreasing pulmonary vascular resistance.
4. Limiting pulmonary vasoconstriction through ventilation with high inspired oxygen concentrations (100% FiO_2), increased tidal volume, and optimal positive end-expiratory pressure ventilation.

Modified from Stobierska-Dzierzek B, Awad H, Michler RE. The evolving management of acute right-sided heart failure in cardiac transplant recipients. *J Am Coll Cardiol* 2001;38(4):923–931.

and tricuspid valve insufficiency. Patients who are bridged to heart transplant with MCS are at increased risk for perioperative RV failure because of the technically more challenging surgical approach, increased blood product requirements, and prolonged ischemic time. Focal cardiac tamponade, acute respiratory distress syndrome (ARDS), and the presence of pulmonary hypertension can all cause acute RV failure. The failing RV often results in worsening venous congestion and subsequent renal, hepatic, and intestinal dysfunction. Treatment of RV failure includes volume optimization, inotropic support, afterload reduction, and mechanical circulatory support. Inhaled nitric oxide (iNO) is commonly used postoperatively for heart transplant patients with elevated pulmonary pressures and RV dysfunction. The normal dose of iNO is 20 to 40 ppm and is typically weaned off prior to extubation. iNO can be very effective in the short term but has limitations with longer-term use. Therefore, other modalities to unload the right ventricle (such as milrinone, isoproterenol, nesiritide, and sildenafil) are also utilized.

Primary Graft Dysfunction

Primary graft dysfunction (PGD), compared to secondary graft dysfunction, occurs when there is no discernible cause (such as hyperacute rejection or pulmonary hypertension) leading to RV failure. In 2013, the ISHLT held a consensus conference on PGD to better define the clinical condition and its management.[58] PGD can involve the isolated RV, LV, or manifest as biventricular dysfunction. It is graded with a 3-tier grading system: mild, moderate, or severe. Risk factors for the development of PGD involve donor, recipient, and surgical factors. Box 48.8 provides a comprehensive list of risk factors. Universal acceptance of the PGD definition has allowed the development of targeted treatment modalities with the goal of reducing mortality (Table 48.3). While the management of PGD is predominantly supportive with escalation of appropriate inotropic and mechanical support, there may be a role for therapies such as plasmapheresis that require future study. Until then, intensivists should focus on preventing PGD from occurring. Box 48.9 describes several preventive measures to decrease the incidence of PGD.

Nephrotoxicity

Kidney function is a major predictor of both mortality on the waiting list and 1-year mortality after transplant. Studies have demonstrated that for every 1 mg/dL increase in creatinine, there is a 58% increase in graft failure at 1 year.[59] Data from the UNOS registry suggest a serum creatinine greater than 2.5 is associated with twice the mortality risk at 1 year. Acute kidney injury (AKI) is commonly encountered in the CICU following heart transplantation. Over 30% of patients develop clinically significant AKI following cardiac surgery.[60] The pathophysiology of AKI following cardiac surgery is multifactorial, including, but not limited to, cellular ischemia leading to tubular and vascular endothelial injury, loss of autoregulation of glomerular filtration rate at

BOX 48.8 Risk Factors for Development of Primary Graft Dysfunction

Donor Risk Factors
Age
Cause of death
Trauma
Cardiac dysfunction
Inotropic support
Comorbidities: diabetes, hypertension
Downtime of cardiac arrest
Drug abuse: alcohol, cocaine, amphetamines
Left ventricular hypertrophy
Valvular disease
Hormone treatment
CAD/wall motion abnormalities on TTE
Sepsis
Alternate list/marginal donor allocation—not increased risk
Troponin trend
Hypernatremia

Recipient Risk Factors
Age
Weight
Mechanical support
Congenital heart disease as etiology of heart failure
Multiple reoperations
LVAD explant
Comorbidities: renal dysfunction, liver dysfunction (high MELD), DM
Ventilator dependent
Multiorgan transplant
Elevated PVR
Allosensitization
Infection
Retransplant

Surgical Procedural Risk Factors
Ischemia time
Donor-recipient sex mismatch
Weight mismatch
Noncardiac organ donation
Experience of procurement team and center volume
Cardioplegic solution
Increased blood transfusion requirement
Elective vs. emergency transplant

Donation of all noncardiac organs, with the exception of lung donation, was associated with decreased incidence of PGD using data from the UNOS. Alternative study shows a high degree of correlation between heart and lung PGD in patient undergoing a paired transplant.
Single-center study showed an incidence of 36% of PGD in the group that received an emergency heart transplant, whereas the incidence was 16% in those for which the transplant was done electively.
CAD, Coronary artery disease; *DM*, diabetes mellitus; *LVAD*, left ventricular assist device; *MELD*, Model for End-stage Liver Disease; *PGD*, primary graft dysfunction; *PVR*, peripheral vascular resistance; *TTE*, transthoracic echocardiogram; *UNOS*, United Network for Organ Sharing.
Modified from Kobashigawa J, Zuckermann A, Macdonald P, et al. Report from a consensus conference on primary graft dysfunction after cardiac transplantation. *J Heart Lung Transplant*. 2014;33(4):327.

TABLE 48.3 Definition of Severity Scale for Primary Graft Dysfunction (PGD)

1. PGD-left ventricle (PGD-LV):	*Mild PGD-LV: One* of the following criteria must be met: *Moderate PGD-LV:* Must meet one criterion from I *and* another criterion from II: *Severe PGD-LV:*	I. LVEF ≤40% by echocardiography, *or* II. Hemodynamics with RAP >15 mm Hg, PCWP >20 mm Hg, CI <2.0 L/min/m^2 (lasting >1 h) requiring low-dose inotropes I. *One* criterion from the following: i. Left ventricular ejection fraction ≤40%, *or* ii. Hemodynamic compromise with RAP >15 mm Hg, PCWP >20 mm Hg, CI <2.0 L/min/m^2, hypotension with MAP <70 mm Hg (lasting >1 h) II. *One* criterion from the following: i. High-dose inotropes: Inotrope score >10 *or* ii. Newly placed IABP (regardless of inotropes) Dependence on left or biventricular mechanical support, including ECMO, LVAD, BiVAD, or percutaneous LVAD. Excludes requirement for IABP.
2. PGD-right ventricle (PGD-RV):	Diagnosis requires either both I and ii, or iii alone:	i. Hemodynamics with RAP >15 mm Hg, PCWP <15 mm Hg, CI <2.0 L/min/m^2 ii. TPG <15 mm Hg and/or pulmonary artery systolic pressure <50 mm Hg, *or* iii. Need for RVAD

BiVAD, Biventricular assist device; *CI*, cardiac index; *ECMO*, extracorporeal membrane oxygenation; *IABP*, intraaortic balloon pump; LVAD, left ventricular assist device; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; RVAD, right ventricular assist device; TPG, transpulmonary pressure gradient.
Inotrope score = dopamine (×1) + dobutamine (×1) + amrinone (×1) + milrinone (×15) + epinephrine (×100) + norepinephrine (×100) with each drug dosed in μg/kg/min.
Modified from Kobashigawa J, Zuckermann A, Macdonald P, et al. Report from a consensus conference on primary graft dysfunction after cardiac transplantation. *J Heart Lung Transplant*. 2014;33(4):327.

BOX 48.9 Preventive Measures to Reduce Primary Graft Dysfunction

- Improved donor management
- Better matching of donor to recipient
- Better preservation
- Gradual wean of inotropes
- Increase use of nitric oxide
- Decrease ischemic time
- Decrease transfusion requirements
- Improved procurement techniques
- Improve recipient selection

Modified from Kobashigawa J, Zuckermann A, Macdonald P, et al. Report from a consensus conference on primary graft dysfunction after cardiac transplantation. *J Heart Lung Transplant*. 2014;33(4):327.

mean arterial blood pressures less than 80 mm Hg, initiation of a systemic inflammatory response, and hemolysis-related kidney injury due to the generation of plasma-free hemoglobin and iron. Furthermore, anemia, red blood cell (RBC) transfusions, and the need for surgical reexploration can potentiate AKI. Preservation of kidney function and maintenance of adequate urine output is one of the most critical jobs of the cardiac intensivist. In the setting of escalating dosages of diuretics, there may be a role for short-term nesiritide to promote diuresis and maintain urine output. Intensivists must avoid nephrotoxic medications, prevent hypotensive episodes, and maintain euvolemia to help ensure successful recovery of kidney function following heart transplantation. Preservation of kidney function allows for optimization of immunosuppression and enhances graft survival. Despite best efforts, transplant patients may require continuous renal replacement therapy (CRRT) or even intermittent hemodialysis (IHD). Most patients will regain renal function within 6 months. Long-term hemodialysis can significantly decrease quality of life. Individuals with an eGFR less than 30 prior to transplant should be considered for dual organ (heart/kidney) transplantation.

IMMUNOSUPPRESSION: EARLY VERSUS LATE

The adaptive immune system is a highly modifiable, specialized, and effective defense system. When targeted appropriately, the adaptive immune system helps to preserve human life. If inappropriately targeted, it can lead to the demise of an individual and a transplanted organ. The amplification of the immune system begins at the moment of the first surgical incision. Tissue factors trigger the upregulation of cytokines that increase the production of both cellular and humoral components of the immune system. The immune system becomes primed to target and destroy anything foreign. Even the most identical donor/recipient matched organ carries the risk for rejection for the life of the recipient. A recipient's immune system will constantly survey the donor heart for markers (antigens) that would identify it as foreign.

The strategy adopted by most transplant centers is early use of multiple drugs that sequentially and synergistically decrease the chance of rejection while attempting to reduce the overall toxicity and side effects of the medications. Immunosuppression may be divided into "early" and "maintenance" immunosuppression. Early immunosuppression refers to therapeutics used at the time of transplantation. Maintenance immunosuppression is often started within hours of heart transplantation but is continued long term. There is considerable overlap between early immunosuppression regimens and treatment for established rejection episodes. The commonly used drugs are listed in Table 48.4.

TABLE 48.4 Pharmacology of Commonly Used Immunosuppressive Agents

Agent	Mechanism of Action	Administration	Toxicity
Antithymocyte globulin (ATG) Both rabbit- and equine-derived preparations available ***Induction Therapy***	Targets multiple epitopes on T-cells, leading to a significant reduction in functional T-cell immunity, plasma cells, and NK cells[67]	IV Infusion rATG can be dosed at 1.5 mg/kg for 5–7 days for a total 7.5 mg/kg Equine antithymocyte globulin (ATGAM) can be dosed 10–15 mg/kg/day	Anaphylaxis Serum sickness Toxic epidermal necrolysis Leukopenia Thrombocytopenia Hemolysis Infection Fevers/rigors
Basiliximab ***Induction Therapy***	Chimeric antibody receptor antagonist of interleukin 2 (IL-2). Disrupts lymphocyte proliferation	IV 20 mg on POD 0 and POD 4 Retrospective analysis comparing ATG and basiliximab showed worsened long-term survival at 5 and 10 years in the basiliximab group[68]	Infection Lymphoproliferative disorders Leukopenia Polycythemia Diabetes mellitus Anaphylaxis Capillary leak syndrome
Cyclosporine	Binds to cyclophilin, inhibits calcineurin-dependent transcription and translation of cytokine genes, particularly interleukin (IL)-2	PO or IV Oral to IV dose adjustment is 3:1 Oral dosage 3-6 mg/kg/day Targeted to 12-hour trough level	Renal dysfunction Hypertension Gingival hyperplasia Hirsutism Tremor Headache Paresthesias Flushing
Tacrolimus	Binds to FK-binding protein, inhibits calcineurin-dependent transcription and translation of cytokine genes, particularly IL-2	PO or IV Oral to IV dose adjustment is 5:1 Oral dosage 0.05–0.15 mg/kg/day Targeted to 12-hour trough level	Renal dysfunction Hypertension Tremor Headache Hypomagnesemia Hyperkalemia Flushing Paresthesias Glucose intolerance
Azathioprine	Inhibits purine ring biosynthesis, decreasing synthesis of DNA and RNA	PO or IV No significant oral to IV adjustment Oral dosage 1–2 mg/kg/day White blood cell (WBC) count to remain >4000/mm^3	Macrocytic anemia Leukopenia Pancreatitis Cholestatic jaundice Hepatitis
Mycophenolate mofetil	Inhibits inosine monophosphate dehydrogenase, inhibiting the de novo pathway for guanine nucleotide biosynthesis	PO or IV No significant oral to IV adjustment Oral dosage 2000–3000 mg/day	Gastrointestinal distress Leukopenia
Sirolimus	Binds to FK-binding protein, inhibits IL-2- and IL-6-driven events	PO Oral dosage 0.5–2 mg/day Targeted to 24-hour trough level	Oral ulcers Dyslipidemias Poor wound healing Bone marrow suppression Lower extremity edema Pleural and pericardial effusions Pulmonary toxicities Nephrotoxicity
Everolimus	Binds to FK-binding protein, inhibits IL-2- and IL-6-driven events	PO Oral dosage 1.5 mg/day divided into 2 doses	Similar to sirolimus but less severe wound healing impairment
Corticosteroids	Lymphocytolysis, inhibits release and action of various interleukins, interferes with antigen receptor interactions	PO or IV with methylprednisolone Oral dosage 0.0–0.1 mg/kg/day divided into 2 doses, which is then tapered to daily	Cushingoid habitus Glucose intolerance Hyperlipidemia Hypertension Cataracts Myopathy Osteoporosis Poor wound healing Salt and water retention Peptic ulcer disease

Modified from Yamani MH, Taylor DO. Heart Transplantation. Cleveland Clinic Center for Continuing Education. August 2010. http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/cardiology/heart-transplantation/. Accessed October 31, 2017.

Early: Induction Versus Noninduction

Early immunosuppression in highly sensitized patients (with elevated levels of circulating antibodies to class I/class II human leukocyte antigens) may begin prior to heart transplantation; these patients are often referred for desensitization therapy. These individuals are at highest risk for the development of rejection. Certain transplant centers specializing in desensitization have implemented protocols that focus on reducing an individual's level of sensitization. Current desensitization strategies include bortezomib, plasmapheresis, rituximab, and IVIG. New studies are looking at the use of monoclonal antibodies such as eculizumab in highly sensitized individuals. The goal is to decrease the likelihood of rejection and, ultimately, to improve long-term survival.

Heart transplant patients typically receive high-dose steroids at the time of transplantation followed by a relatively slow taper. Approximately 50% of transplant programs utilize induction therapy. The decision to use induction therapy balances the risk of increased infection against the benefit of potentially decreased rejection. Individuals at a higher risk for rejection typically will undergo induction therapy, most commonly with ATG.

Transplant recipients typically receive standard triple therapy immediately following surgery. Standard triple drug therapy consists of a calcineurin inhibitor (CNI; most commonly tacrolimus, with less use of cyclosporine), an antiproliferative (mycophenolate mofetil, mycophenolic acid, or azathioprine), and steroids. Many transplant programs have a renal-sparing protocol for patients with underlying renal dysfunction. Induction therapy with ATG allows the clinician to safely withhold the calcineurin inhibitor for the first 3 to 5 days in an effort to avoid nephrotoxicity.

As immunosuppression regimens transition from early to maintenance therapy, immunosuppressive medications are weaned to target lower therapeutic drug levels and reduce the risk of associated morbidity. Approximately 50% of patients are weaned off of corticosteroids by 1 year.

Maintenance

The first year of maintenance immunosuppression is driven, in part, by biopsy results, echocardiographic findings, and patient tolerance of medications. Typical maintenance therapy will include tacrolimus, mycophenolate, and low-dose prednisone. Some individuals are switched to proliferation signal inhibitors (PSIs), such as sirolimus or everolimus, instead of antiproliferative agents once adequate wound healing has occurred. There are multiple indications to switch to a PSI, which are discussed later. PSI use is discouraged in the first 6 months given their association with poor wound healing and significant nephrotoxicity. Newer laboratory tests, such as a T-cell immune function assay, may hold promise in allowing clinicians to target the lowest effective doses of immunosuppressive medications. This strategy promises to reduce the complications and side effects associated with higher dosages of the medications. Once a patient has stabilized on an outpatient maintenance regimen, the incidence of rejection drops dramatically between years 1 and 3.[61]

LONG-TERM COMPLICATIONS OF HEART TRANSPLANTATION

Cardiac Allograft Vasculopathy

When patients present with LV dysfunction and a negative workup for rejection, the diagnosis of cardiac allograft vasculopathy (CAV) must be considered. CAV is a unique process with a pathophysiology different from traditional atherosclerosis. CAV occurs along a spectrum but continues to be a leading cause of long-term mortality beyond the first postoperative year.[63] The development of CAV within the first 12 months confers a much higher mortality compared to individuals with no evidence of CAV. Early CAV is typically a diffuse process, affecting the distal vessels in the coronary vascular bed with little hope for successful intervention. Late development of CAV is much more likely to involve the proximal vessels and to be focal in nature. The pathophysiology suggests that both acute and chronic rejection play a significant role in the development of CAV. While many programs have various prophylactic regimens for CAV, the guidelines provide class I recommendations only for statin therapy and strict control of cardiovascular risk factors.[62] The treatment of CAV with percutaneous intervention and, in rare situations, coronary bypass surgery is largely dependent on lesion location and length. Treatment beyond revascularization includes optimization of immunosuppression and the use of PSIs. Sirolimus and everolimus decreased progression of CAV; CAV is a clear indication to switch a patient from antimetabolites to PSIs. Patients with progressive CAV may develop such severe graft dysfunction that retransplantation is the only therapeutic option.

Infection

Infections are a common complication following heart transplantation. Recognizing the duration of time from transplant, the degree of posttransplant immunosuppression, and the presence of intravascular devices can assist in generating a differential diagnosis. Although a transplant recipient is at an increased risk of unusual infections, the microbiology is generally dictated by the time from transplant (Fig. 48.5).[63] In general, infections that trigger an acute decompensation causing septic shock are usually bacterial in nature, with the possible exception of influenza. Although bacteremia is common, the mortality in this population is not higher than in the nontransplant population, likely due to the increased vigilance resulting in earlier identification and the blunted host inflammatory response.[64,65]

Recent health care contact and antibiotic exposure influences the likelihood of resistant gram-positive organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococcus (VRE), and resistant gram negatives such as *Pseudomonas* and *Acinetobacter*. VRE infrequently causes severe illness; broad spectrum antibiotic therapy with vancomycin and a β-lactam agent with antipseudomonal activity should be considered to be first-line treatment. If the local microbiology has a high percentage of extended-spectrum β-lactamase (ESBL) producers, consideration should be given to a carbapenem as the β-lactam. The presence of indwelling central venous catheters or other endovascular devices warrant MRSA coverage with vancomycin. Additionally, the presence of these devices may

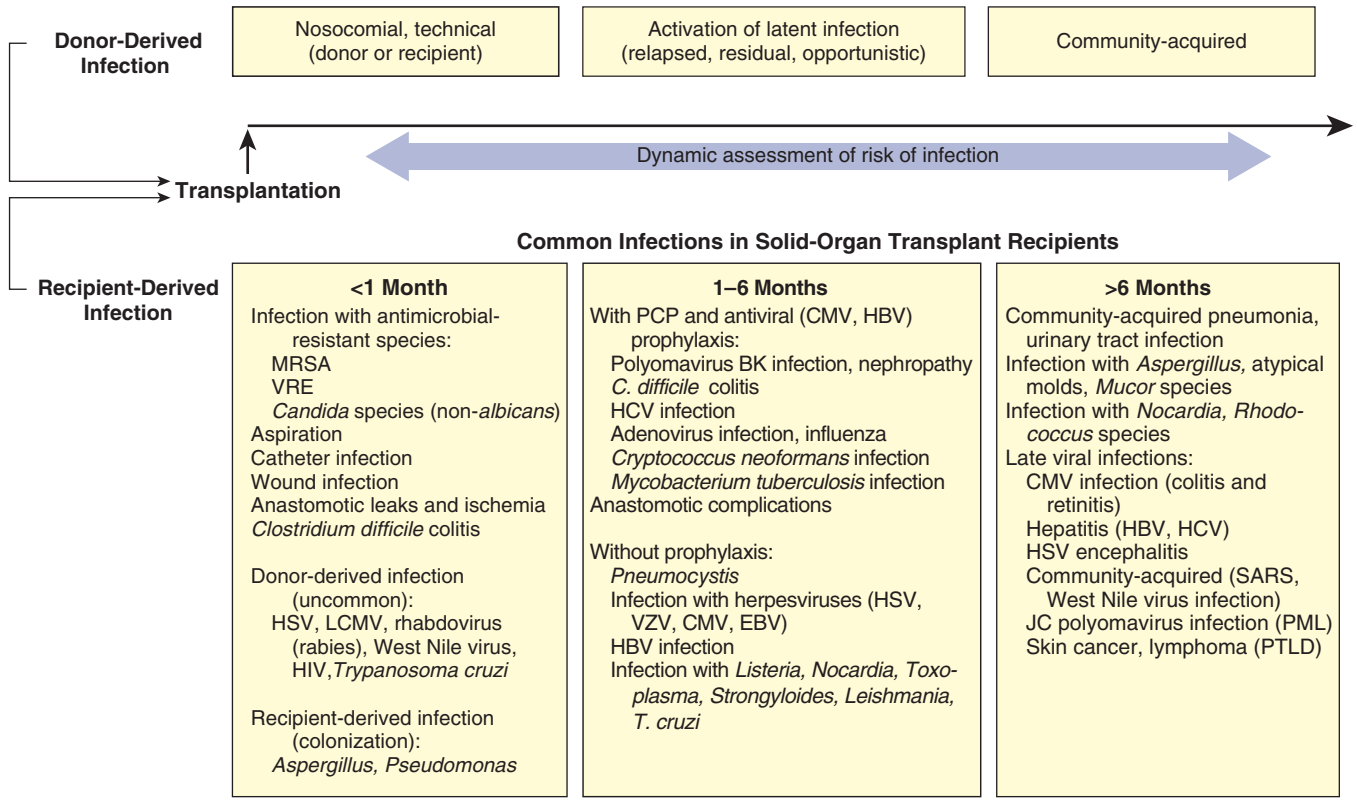

Fig. 48.5 Changing timeline of infection after organ transplantation. Infections occur in a generally predictable pattern after solid-organ transplantation. The development of infection is delayed by prophylaxis and accelerated by intensified immunosuppression, drug toxic effects that may cause leukopenia, or immunomodulatory viral infections, such as infection with cytomegalovirus (CMV), hepatitis C virus (HCV), or Epstein-Barr virus (EBV). At the time of transplantation, a patient's short-term and long-term risk of infection can be stratified according to donor and recipient screening, the technical outcome of surgery, and the intensity of immunosuppression required to prevent graft rejection. Subsequently, an ongoing assessment of the risk of infection is used to adjust both prophylaxis and immunosuppressive therapy. *HBV,* Hepatitis B virus; *HIV,* human immunodeficiency virus; *HSV,* herpes simplex virus; *LCMV,* lymphocytic choriomeningitis virus; *MRSA,* methicillin-resistant *Staphylococcus aureus*; *PCP, Pneumocystis carinii* pneumonia; *PML,* progressive multifocal leukoencephalopathy; *PTLD,* posttransplantation lymphoproliferative disorder; *SARS,* severe acute respiratory syndrome; *VRE,* vancomycin-resistant *Enterococcus faecalis*; *VZV,* varicella-zoster virus. (Modified from Fishman JA. Infection in solid-organ transplant recipients. *N Engl J Med.* 2007;357[25]:2601–2614.)

justify empiric antifungal treatment with an echinocandin. An extensive history of antibiotic exposure, intraabdominal surgery, or total parenteral nutrition use dramatically increases the incidence of candidemia.

The early posttransplant period is the highest risk period for development of opportunistic infections. Immunosuppressive regimens are most intense during the first 6 months after transplant; the use of prophylaxis has significantly reduced the burden of opportunistic infection. Common prophylactic regimens include valganciclovir for cytomegalovirus (CMV), trimethoprim-sulfamethoxazole for *Pneumocystis jiroveci* (PCP), fluconazole for coccidioidomycosis, and nystatin swish and swallow for oral candidiasis. Fungal infections peak in the 2 months after transplant and most commonly occur in individuals who were recently treated with broad spectrum antibiotics. During months 6 through 12, infection is largely related to common community-acquired pathogens. Patients presenting with shortness of breath, cough, and infiltrates on chest radiographs at 12 months have most likely developed community-acquired pneumonia, whereas at 3 months, opportunistic infections are much more common.

In subacute presentations, the type and degree of immunosuppression used, any recent increase in immunosuppression, and the time from transplant must be used to assess the risk of unusual pathogens. Care must also be taken to consider noninfectious etiologies in these patients with multiple reasons to have sepsis-like syndromes.

Arrhythmias

Late-onset atrial arrhythmias can represent an underlying episode of rejection. Syncope and palpitations should be taken very seriously in this patient population. Severe cases of rejection

TABLE 48.5 International Society for Heart and Lung Transplantation Standardized Cardiac Biopsy Grading: Acute Cellular Rejection

Grade	Description	Prior Classification
0R	No rejection	0
1R, mild	Interstitial and/or perivascular infiltrate with up to one focus of myocyte damage	1A, 1B, 2
2R, moderate	Two or more foci of infiltrate with associated myocyte damage	3A
3R, severe	Diffuse infiltrate with multifocal myocyte damage ± edema ± hemorrhage ± vasculitis	3B, 4

Modified from Stewart S, Winters GL, Fishbein MC, et al. Revision of the 1990 Working Formulation for the Standardization of Nomenclature in the Diagnosis of Heart Rejection. *J Heart Lung Transplant.* 2005;24:1710-1720.

TABLE 48.6 Diagnosis of Antibody-Mediated Rejection

Histology \ Immunopathology	–	+
–	pAMR0 *Negative*	pAMR1i *Suspicious*
+	pAMR1h *Suspicious*	pAMR2 *Positive* pAMR3 *Severe*

The grading scheme stratifies biopsies based on no histologic or immunologic evidence of antibody-mediated rejection (negative, pAMR0); either histologic or immunologic evidence of antibody-mediated rejection (suspicious, pAMR1h or pARMi, respectively); both histologic and immunologic evidence of antibody-mediated rejection (positive, pAMR2); and a final category for severe findings of myocardial destruction (pAMR3).
Modified from Kittleson MM, Kobashigawa JA. Long-term care of the heart transplant recipient. *Curr Opin Organ Transplant.* 2014;19:515–524.

may manifest as bradyarrhythmias with the potential for progression to cardiac arrest and/or asystole. Conduction abnormalities may be present in cases of CAV and/or significant cardiac fibrosis. Ventricular arrhythmias are rarely encountered after heart transplantation, but their development can be ominous. New-onset ventricular arrhythmias may be the first representation of CAV or acute rejection. Every heart transplant patient presenting with a new arrhythmia should undergo thorough evaluation.

Rejection: Acute Cellular Versus Antibody Mediated

The majority of heart transplant recipients demonstrate normal LV and RV function at the time of discharge. Any decrease in cardiac function, whether accompanied by symptoms or not, must be taken seriously and thoroughly evaluated. There are two major causes of decreased cardiac function after transplant: cardiac allograft rejection and cardiac allograft vasculopathy. Patients suffering from acute rejection present with a wide variety of symptoms and clinical findings. If rejection is suspected, aggressive treatment should be initiated as soon as possible, as these patients can quickly decompensate. The gold standard for diagnosing rejection is an endomyocardial biopsy but the sensitivity is limited and results may not be confirmed for up to 72 hours. Waiting for the tissue diagnosis in this patient population before treating is discouraged, as patients may die from a potentially treatable rejection episode.

There are three major types of rejection: hyperacute rejection (discussed earlier), acute cellular rejection (ACR), and antibody-mediated rejection (AMR). Revised grading systems have been adopted by the ISHLT in an effort to standardize definitions. These grading systems are based on histologic grade, including endothelial activation with intravascular macrophages and immunopathology (deposition of complement and human leukocyte antigen) in AMR (Tables 48.5 and 48.6).

Several factors must be considered when there is suspicion of acute rejection:

- Is there ventricular dysfunction?
- Is the patient symptomatic?
- Is there a history of rejection?
- What is the time from transplantation?
- What are the current doses of immunosuppressive agents?
- Are the levels of immunosuppressive agents therapeutic?

Table 48.7 reviews current treatment recommendations for both acute cellular and antibody-mediated rejection.

Side Effects of Immunosuppression: Malignancy, Nephrotoxicity, Drug-Drug Interactions

Major limitations in the field of transplantation are related to the sequelae of chronic immunosuppression. Immunosuppressive drugs decrease the risk of rejection and treat established rejection, but at a price.[66] Starting in years 2 to 3 following transplantation, the incidence of malignancy begins to increase; by year 5, it becomes the leading cause of death. Studies have demonstrated a 2- to 4-fold increase in the incidence of malignancy in heart transplant patients compared to kidney transplant recipients. This likely represents the difference in the degree of immunosuppression required to prevent rejection in the heart and the kidney. The current strategy includes the transition from CNIs and antimetabolites to the use of a PSI, which has been demonstrated to reduce both the incidence and progression of malignancy.

In addition to the side effects of immunosuppression, it is important that the cardiac intensivist is aware of the drug-drug interactions that occur in patients on chronic immunosuppression. Box 48.10 demonstrates how immunosuppression levels are affected by various drugs.

FUTURE DIRECTIONS

Research to address the supply and demand mismatch between donors and potential recipients is generating exciting discoveries in organ preservation techniques, which may result in an increased donor pool. New pharmacotherapeutics hold the promise of

TABLE 48.7 Treatment of Acute Cellular and Antibody-Mediated Rejection

	Asymptomatic	Reduced EF	Heart Failure/Shock
Cellular rejection	Target higher CNI levels Oral steroid bolus + taper MMF → PSI	Oral steroid bolus/taper *or* IV pulse steroids	*Treat based on clinical presentation; do not wait for biopsy findings* IV pulse steroids Cytolytic therapy (ATG) Plasmapheresis (before ATG dose) IV immunoglobulin Inotropic therapy IV heparin IABP or ECMO support
Antibody-mediated rejection with no or decreased DSA	Target higher CNI levels MMF → PSI	IV pulse steroids Consider IV immunoglobulin	
Antibody-mediated rejection with increased DSA	Oral steroid bolus + taper MMF → PSI Consider IV immunoglobulin and rituximab	IV pulse steroids IV immunoglobulin Consider ATG, rituximab, or bortezomib	

ATG, Antithymocyte globulin; *CNI,* calcineurin inhibitor; *DSA,* donor-specific anti-human leukocyte antigen antibodies; *ECMO,* extracorporeal membrane oxygenation; *EF,* ejection fraction; *IABP,* intraaortic balloon pump; *IV,* intravenous; *MMF,* mycophenolate mofetil; *PSI,* proliferation signal inhibitor.

Modified from Kittleson MM, Kobashigawa JA. Long-term care of the heart transplant recipient. *Curr Opin Organ Transplant*. 2014;19:515–524.

BOX 48.10 Drugs That Affect the Levels of Tacrolimus, Cyclosporine, Sirolimus, and Everolimus

Decrease Immunosuppression Levels

Antiepileptics

Carbamazepine
Fosphenytoin
Phenobarbital
Phenytoin

Antiretrovirals

Efavirenz
Etravirine
Nevirapine

Other

Antacids containing magnesium, calcium, or aluminum (tacrolimus only)
Deferasirox
Modafinil
St. John's wort
Thalidomide
Ticlopidine
Troglitazone

Increase Immunosuppression Levels

Antimicrobials

Clarithromycin
Erythromycin
Metronidazole and tinidazole
Quinupristin/dalfopristin
Levofloxacin

Antifungals

Clotrimazole
Itraconazole
Ketoconazole
Fluconazole
Posaconazole
Voriconazole

Antiretrovirals

Protease inhibitors (general)
Amprenavir
Atazanavir
Darunavir
Fosamprenavir
Indinavir
Nelfinavir
Ritonavir
Saquinavir
Tipranavir

Modified from Costanzo MR, Dipchand A, Starling R, et al. The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients, *J Heart Lung Transplant*. 2010;29(8):914–956.

decreasing episodes of rejection without increasing the risk for infection. Identification of biomarkers allowing for earlier detection of rejection are actively being developed. Improved techniques to optimize donor-recipient immunologic matching to help further reduce the risk of rejection are showing significant promise. Technological advances allowing for improved mechanical support options will decrease waiting list mortality for AHF patients. While the field awaits exciting future discoveries, a focus on improved candidate selection and meticulous pre- and post-transplant management will improve outcomes and the quality of life for AHF patients.

Acknowledgments

We thank Dale G. Renlund, Brad Y. Rasmusson, Patrick W. Fisher, and Abdallah G. Kfoury, who contributed to this chapter in previous editions of the book.

The full reference list for this chapter is available at ExpertConsult.com.

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