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Management of the ACC/AHA Stage D Patient
Cardiac Transplantation

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KEYWORDS

• Cardiac transplantation • End-stage heart failure • Rejection • Immunosuppression

KEY POINTS

- Heart transplantation is indicated in patients with heart failure despite optimal medical and device therapy, manifesting as intractable angina, refractory heart failure, or intractable ventricular arrhythmias.
- The evaluation for heart transplantation focuses on assessment of the presence of optimal medical management, the stability of extracardiac function, and adequate compliance and caregiver support.
- Standard immunosuppression after transplantation consists of triple-drug therapy with corticosteroids, calcineurin inhibitors (most commonly tacrolimus), and antiproliferative agents (most commonly mycophenolate mofetil).
- Treatment of rejection is progressively more aggressive as the patient's clinical status worsens, and ranges from an oral corticosteroid bolus and taper to intravenous pulse corticosteroids, cytolytic therapy with antithymocyte globulin, intravenous immune globulin, plasmapheresis, and circulatory support with inotropic therapy, intra-aortic balloon counterpulsation, and extracorporeal membrane oxygenation.
- The major long-term complications of heart transplantation are cardiac allograft vasculopathy, infections, and malignancy.

INTRODUCTION

Despite advances in pharmacologic and device treatment of chronic heart failure, long-term morbidity and mortality remain unacceptably high, with many patients progressing to end-stage heart failure. The 5-year mortality for patients with symptomatic heart failure approaches 50%, and may be as high as 80% at 1 year for the end-stage patients.[1] Over the last 4 decades, cardiac transplantation has become the preferred therapy for select patients with end-stage heart disease. Approximately 2400 heart transplants are performed annually in the United States. According to the registry of the International Society of Heart and Lung Transplantation, the median survival of patients after transplantation is currently 10 years, and up to14 years for those surviving the first year (**Fig. 1**), a significant improvement over that of medical therapy for heart failure.[2]

The purpose of this article is to provide an overview of heart transplantation in the current era, focusing on the evaluation process for heart transplantation, the physiology of the transplanted heart, immunosuppressive regimens, and early and long-term complications.

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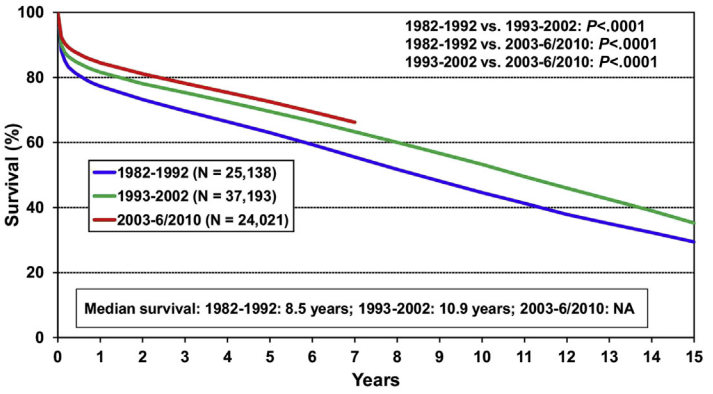

Fig. 1. Survival by era from the International Society of Heart and Lung Transplantation Registry. The median survival for the cohort of 96,273 adult and pediatric heart recipients who completed at least 1 year of follow-up is 10 years. For patients who survive the first year, the half-life is 14 years. When survival is stratified by the era of transplant, there has been a continued improvement in survival over the past 3 decades. (*From* Stehlik J, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: 29th official adult heart transplant report—2012. J Heart Lung Transplant 2012;31(10):1056; with permission.)

EVALUATION FOR HEART TRANSPLANTATION

Indications

The 3 major indications for heart transplantation are heart failure, angina, and ventricular arrhythmias refractory to maximal medical therapy. The most common indication for heart transplantation is refractory heart failure. Angina alone is often not considered an indication for transplantation in the absence of heart failure, as it is not clear if the survival of such patients is improved with heart transplantation. Intractable ventricular arrhythmias, commonly referred to as "VT storm," may merit heart transplant evaluation, and often urgent listing, given the association with hemodynamic compromise. The relative scarcity of donor organs makes it essential to determine whether patients are truly refractory to maximal medical therapy and require heart transplantation (**Fig. 2**).

Objective measurements that may help stratify the severity of illness include cardiopulmonary exercise stress testing and right heart catheterization. The cardiopulmonary exercise stress test measures maximal oxygen consumption (Vo_2max), which is proportional to cardiac output. A compensated patient with a Vo_2max of 12 to 14 mL/kg/min with adequate effort indicates poor survival over the next year and is an indication to proceed with evaluation.[3] Adequate effort is defined as the patient's achievement of anaerobic threshold, at which point CO_2 production exceeds O_2 consumption (indicated by respiratory exchange ratio [RER] >1).

Performing right heart catheterization once the patient is euvolemic is helpful in assessing the degree of fixed postcapillary pulmonary hypertension and cardiac output at rest. A cardiac index value of less than 2.5 L/min/m^2 suggests poor reserve and the need for transplant evaluation.[4]

Contraindications

The 2 major contraindications for heart transplantation are medical and social/psychological. The standard testing for the heart transplant evaluation is outlined in **Box 1**, and the potential contraindications are described in detail in **Table 1**. Many of these factors are not absolute, and need to be considered in the context of the severity of the patient's heart disease and associated comorbidities.

PHYSIOLOGY OF THE TRANSPLANTED HEART

Lack of Innervation to the Transplantation Heart

When the donor heart is placed into the recipient, both afferent (from the heart to the central nervous system) and efferent (from the central nervous system to the heart) nerve supply is lost. The loss of afferent nerve supply means that the recipient will not experience angina. Therefore, chest discomfort in a heart transplant recipient, especially early after transplant, is likely not caused by coronary ischemia, and coronary ischemia will likely not present with chest discomfort. The standard practice of annual angiograms for surveillance of transplant coronary artery disease is a direct consequence of the lack of afferent nerves supplying the transplanted heart.

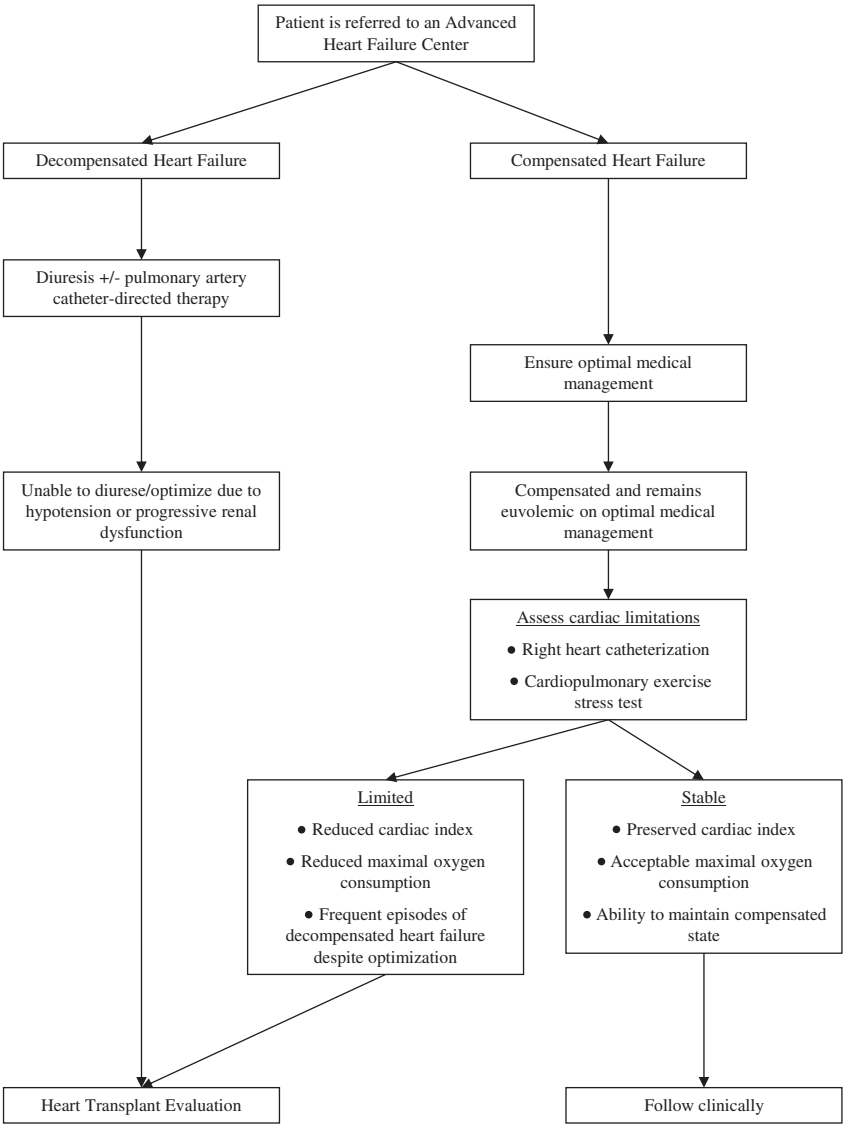

Fig. 2. Clinical algorithm to determine whether patients with advanced heart failure are limited enough to merit heart transplant evaluation. (*From* Kittleson MM, Kobashigawa JA. Management of advanced heart failure: the role of heart transplantation. Circulation 2011;123(14):1570; with permission.)

The consequences of the loss of efferent nerves are related to the loss of vagal tone and the postganglionic direct release of norepinephrine stores in response to exercise. With the loss of vagal tone, heart transplant recipients have a higher than normal resting heart rate of around 90 to 110 beats per minute. The lack of efferent nerves also means that the transplant recipient must rely on circulating catecholamines to respond to exercise, so there is a blunting of the heart rate's response to exercise. Similarly, after exercise, the heart rate returns to baseline more slowly because of the gradual decline of circulating catecholamine concentrations to baseline.

Heart transplant recipients lack the baroreceptor reflex, which relies on intact baroreceptors and sympathetic and parasympathetic innervation. Thus, heart transplant recipients are more susceptible to orthostasis, and carotid sinus massage will not break a reentrant tachycardia in these patients.

Nevertheless, some heart transplant recipients often experience reinnervation of the heart, with return of angina, an improvement in exercise tolerance, and a decrease in resting heart rate. This

Box 1
Recommended tests for baseline evaluation for heart transplantation

- Weight/body mass index
- Immunocompatibility
  - ABO typing
  - Human leukocyte antigen tissue typing
  - Panel reactive antibodies and flow cytometry
- Assessment of severity of heart failure
  - Cardiopulmonary exercise test
  - Echocardiogram
  - Right heart catheterization
- Evaluation of multiorgan function
  - Routine laboratory work (basic metabolic profile, complete blood count, liver function tests)
  - Urinalysis
  - 24-hour urine collection for protein and creatinine
  - Pulmonary function tests
  - Chest radiograph
  - Abdominal ultrasonography
  - Carotid Doppler (if >50 years or with ischemic heart disease)
  - Ankle-brachial indices (if >50 years or with ischemic heart disease)
  - Dental examination
  - Ophthalmologic examination (if diabetic)
- Infectious serology and vaccination
  - Hepatitis B surface Ag, Ab, core Ab
  - Hepatitis C Ab
  - Human immunodeficiency virus
  - Rapid plasma reagin
  - Immunoglobulin G for herpes simplex virus, cytomegalovirus, toxoplasmosis, Epstein-Barr virus, varicella
  - Purified protein derivative
  - Immunizations: influenza, pneumovax, hepatitis B
- Preventive and malignancy
  - Stool for occult blood × 3
  - Colonoscopy (if indicated or if >50 years)
  - Mammography (if indicated or if >40 years)
  - Papanicolaou smear
  - Prostate-specific antigen and digital rectal examination (men >50 years)
- General consultations
  - Social work
  - Psychiatry
  - Financial
  - As indicated: pulmonology, nephrology, infectious disease, endocrinology

Adapted from Mehra MR, Kobashigawa J, Starling R, et al. Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates—2006. J Heart Lung Transplant 2006;25(9):1036; with permission.

process is inconsistent among patients, although it tends to increase over time.

Response to Medications

Some cardiac drugs are not effective in the denervated heart. Because of the lack of vagal tone, digoxin will have little effect on sinoatrial and atrioventricular conduction velocity, and will not achieve rate control if the transplanted heart develops atrial fibrillation. However, the inotropic effects of digoxin persist after transplantation. Similarly, the parasympatholytic effect of atropine will not increase the heart rate in transplanted hearts. Owing to the lack of baroreceptor reflexes, vasodilators such as nifedipine and hydralazine will not cause reflex tachycardia.

The lack of postganglionic sympathetic nerves in the transplanted heart results in increased receptor density, and thus more sensitivity to sympathetic agonists and antagonists. Clinically this is most often seen with β-blockers; heart transplant recipients will often have exaggerated fatigue and, occasionally, bradycardia in response to administration of β-blockers, especially with exercise.

IMMUNOSUPPRESSION

Induction Therapy

Purpose

The purpose of induction therapy was originally to induce tolerance in the graft. Although this goal has not been realized, the benefits of induction therapy include a marked reduction in rejection in the first 4 to 6 weeks after transplantation, and the ability to delay the introduction of calcineurin inhibitors to prevent worsening renal dysfunction.[5,6] The disadvantages of induction therapy include increased risk of infection, risk of malignancy, and rates of late rejection after therapy is completed.[7] At 1 year, the rejection rates of

Table 1
Contraindications to heart transplantation

Age	>70 y is a relative contraindication depending on associated comorbidities
Obesity	Body mass index (BMI) <30 kg/m^2 is recommended; most centers will tolerate BMI <35 kg/m^2
Malignancy	Active neoplasm, except nonmelanoma skin cancer, is an absolute contraindication; cancers that are low grade (such as prostate) or in remission may be acceptable in consultation with an oncologist
Pulmonary hypertension	The inability to achieve pulmonary vascular resistance <2.5 with vasodilator or inotropic therapy is a contraindication; such patients may benefit from long-term unloading with a ventricular assist device
Diabetes	Uncontrolled diabetes or that associated with significant end-organ damage is an absolute contraindication
Renal dysfunction	If due to diabetes, may be an absolute contraindication
Peripheral vascular disease	Severe disease not amenable to revascularization is an absolute contraindication
Infection	Human immunodeficiency virus and hepatitis C are absolute contraindications at most centers
Substance use	6 mo of abstinence from smoking, alcohol, and illicit drugs is required; in critically ill patients, consultation with psychiatry and social work is essential
Psychosocial issues	Noncompliance, lack of caregiver support, and dementia are absolute contraindications; mental retardation may be a relative contraindication

Adapted from Kittleson MM, Kobashigawa JA. Management of advanced heart failure: the role of heart transplantation. Circulation 2011;123(14):1572; with permission.

patients receiving induction are usually similar to those not receiving induction.

Regimens

Regimens for induction therapy include the cytolytic agent antithymocyte globulin and the interleukin-2 receptor (IL-2R) antagonist dacluzimab (Fig. 3). However, despite widespread use, no randomized trials of cytolytic agents as induction therapy have been performed in heart transplant recipients. Retrospective evaluations from a large, multi-institutional database have suggested that cytolytic therapy reduces the risk of early rejection but increases the risk of infection. In a randomized trial of induction therapy with dacluzimab in heart transplant recipients, such recipients had less rejection but an increased risk of death from infection; because of the blinded nature of the study, some patients received both the IL-2R antagonist and cytolytic induction therapy.[7]

Based on these results, induction therapy is not standard practice at many centers. Instead such therapy, most often with antithymocyte globulin, may be reserved for those patients at the highest risk for rejection, including patients who are highly sensitized with donor-specific antibodies, or those with significant renal dysfunction in whom delay of calcineurin inhibition is advisable.

Maintenance Therapy

The purpose of maintenance immunosuppressive therapy is to prevent long-term rejection in transplant recipients. Triple-drug therapy most commonly consists of steroids, a calcineurin inhibitor such as cyclosporine or tacrolimus, and an antiproliferative agent such as azathioprine or mycophenolate mofetil (MMF) (Table 2). In special situations a proliferation signal inhibitor (PSI), such as sirolimus or everolimus, may replace the calcineurin inhibitor or antiproliferative agent. Although the optimal maintenance immunosuppressive regimen has yet to be identified, there is evidence that regimens may be tailored to the individual patient, as detailed here.

Steroid therapy

Mechanism of action Corticosteroids are potent immunosuppressive and anti-inflammatory agents (see Fig. 3). Corticosteroids diffuse freely across cell membranes and ultimately alter the expression of genes involved in the immune and inflammatory

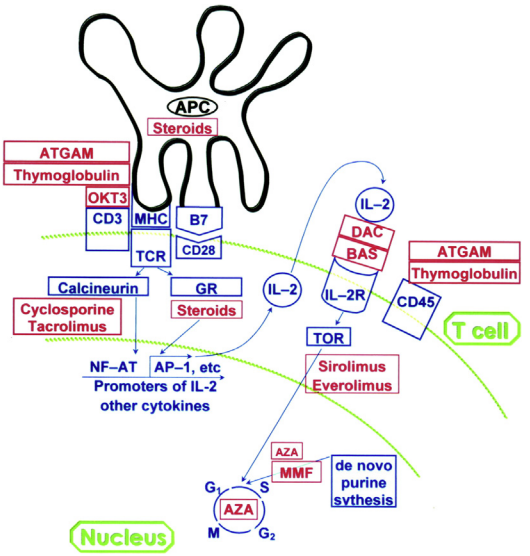

Fig. 3. Immunologic mechanisms leading to graft rejection and sites of action of immunosuppressive drugs. Immunologic mechanisms are shown in blue; immunosuppressive drugs and their site of action are shown in red. Acute rejection begins with recognition of donor antigens that differ from those of recipient by recipient antigen-presenting cells (APCs) (indirect allorecognition). Donor APCs (carried passively in graft) may also be recognized by recipient T cells (direct allorecognition). Alloantigens carried by APCs are recognized by the TCR-CD3 complex on the surface of the T cell. When accompanied by costimulatory signals between APC and T cells such as B7-CD28, T-cell activation occurs, resulting in activation of calcineurin. Calcineurin dephosphorylates transcription factor NF-AT, allowing it to enter the nucleus and bind to promoters of interleukin (IL)-2 and other cytokines. IL-2 activates cell surface receptors (IL-2R), stimulating clonal expansion of T cells (T-helper cells). IL-2, along with other cytokines produced by T-helper cells, stimulates expansion of other cells of the immune system. Activation of IL-2R stimulates target of rapamycin (TOR), which regulates translation of mRNAs to proteins that regulate the cell cycle. Sites of action of individual drugs (highlighted in red) demonstrate multiple sites of action of these drugs, underscoring the rationale for combination therapy. AZA, azathioprine; BAS, basiliximab; DAC, daclizumab; GR, glucocorticoid receptor; MMF, mycophenolate mofetil. (*From* Lindenfeld J, Miller GG, Shakar SF, et al. Drug therapy in the heart transplant recipient: part II: immunosuppressive drugs. Circulation 2004;110(25):3862; with permission.)

response, affecting the number, distribution, and function of all leukocytes.

Administration Corticosteroids are first given as an intravenous bolus of methylprednisolone during the transplant surgery. Oral prednisone is then given in a standard taper, which can differ at various institutions. At the authors' center, patients receive prednisone 40 mg twice daily, decreasing by 5 mg increments until the patient is on 10 mg twice daily. At 1 month after transplantation, the patient will start a prednisone taper so that by 3 months, the prednisone is reduced to 10 mg once daily and by 6 months, decreased to 5 mg once daily. In this program, patients with no rejection in the first 6 months are candidates to be weaned off prednisone completely by 1 year after transplantation.

Side effects Steroid therapy has significant short-term and long-term side effects.[8] Short-term side effects include tremors, emotional lability, easy bruisability, poor wound healing, weight gain, fluid retention, and hyperglycemia. Long-term adverse effects include hypertension, cataracts, ulcer disease, risk of infection, and osteoporosis. Long-term administration of steroids may result in chronic adrenal suppression, and adrenal insufficiency can follow a steroid taper or stress, such as infection or surgery.

Calcineurin inhibitor therapy

Mechanism of action Calcineurin inhibitors have become a cornerstone of maintenance therapy. The 2 calcineurin inhibitors used in clinical practice are cyclosporine and tacrolimus, both of which act by blocking calcium-activated calcineurin (see Fig. 3). Cyclosporine binds to cyclophilin and tacrolimus binds to FK-binding protein. The complex then binds to calcineurin, which dephosphorylates nuclear factor of activated T cells (NF-AT). Dephosphorylated NF-AT then binds to specific DNA sites and ultimately inhibits transcription of interleukin-2 and other cytokines.

Clinical trials Tacrolimus has been compared with cyclosporine in several randomized clinical trials. Both tacrolimus and cyclosporine have demonstrated comparable survival in heart transplantation, but tacrolimus may be associated with less treated rejection.[9,10] Tacrolimus is currently the calcineurin inhibitor of choice for maintenance immunosuppression therapy.

Administration Either cyclosporine or tacrolimus is given orally immediately following surgery. For cyclosporine, the dose is titrated to achieve target therapeutic trough levels of 250 to 350 ng/mL. Over the long term, cyclosporine doses are reduced to achieve target trough levels between 100 and 200 ng/mL. Tacrolimus is titrated to achieve target therapeutic levels of 10 to 15 ng/mL initially postoperatively and, over the longer term, doses are reduced to achieve target levels between 5 and 10 ng/mL. At some centers, higher levels of

Table 2
Maintenance immunosuppression

Class	Mechanism	Drugs	Usage
Corticosteroids	Alter expression of genes involved in the immune and inflammatory response, affecting the number, distribution, and function of all leukocytes	Methylprednisolone Prednisone	For all patients in the first year posttransplant Some patients weaned off after the first 6–12 mo
Calcineurin inhibitors	Cyclosporine binds to cyclophilin and tacrolimus binds to FK-binding protein. The complex then binds to calcineurin, which dephosphorylates NF-AT (nuclear factor of activated T cells). Dephosphorylated NF-AT then binds to specific DNA sites and ultimately inhibits transcription of interleukin-2 and other cytokines	Cyclosporine Tacrolimus	For all patients after transplantation May be stopped because of renal insufficiency and replaced with a proliferation signal inhibitor Tacrolimus is associated with less rejection in clinical trials
Antimetabolites	Azathioprine is converted in cells to a purine analogue incorporated into DNA, thus inhibiting its synthesis and the proliferation of both T and B lymphocytes. Mycophenolate mofetil (MMF) is an inhibitor of a key enzyme in the de novo synthesis of guanine nucleotides. Because proliferating lymphocytes are dependent on this pathway for DNA replication, MMF is a selective inhibitor of lymphocyte proliferation	Azathioprine Mycophenolate mofetil	Azathioprine cannot be given with allopurinol MMF is associated with less rejection in clinical trials
Proliferation signal inhibitors	Sirolimus and everolimus inhibit a kinase, target of rapamycin, ultimately inhibiting proliferation of T and B lymphocytes, smooth muscle cells, and endothelial cells	Sirolimus Everolimus	Only sirolimus is approved by the Food and Drug Administration for use in heart transplant recipients Not recommended for de novo use posttransplant

tacrolimus are targeted in an attempt to reduce the need for corticosteroids and antiproliferative agents.[11]

Side effects Cyclosporine causes nephrotoxicity, hypertension, dyslipidemia, neurologic toxicity, hypertrichosis, and gingival hyperplasia.[8] Tacrolimus has a similar side-effect profile, but does not cause hypertrichosis or gingival hyperplasia; in fact, alopecia may occur. Hyperglycemia and neurologic toxicity are more common with tacrolimus.

Antiproliferative therapy

Mechanism of action Azathioprine and MMF are the antiproliferative agents used most commonly after heart transplantation (see Fig. 3). Azathioprine is ultimately converted in cells to a purine analogue incorporated into DNA, thus inhibiting its synthesis and the proliferation of both T and B lymphocytes. MMF is an inhibitor of a key enzyme in the de novo synthesis of guanine nucleotides. Because proliferating lymphocytes depend on

this pathway for DNA replication (other cells use both de novo and salvage pathways), MMF is a selective inhibitor of lymphocyte proliferation.

Clinical trials A multicenter, randomized clinical trial compared azathioprine and MMF in combination with cyclosporine and steroids, and demonstrated that MMF-treated patients had improved survival, less rejection, and less cardiac allograft vasculopathy over time.[12] MMF is thus the antimetabolite of choice for standard maintenance therapy in heart transplant recipients.

Administration Either azathioprine or MMF is given orally immediately after transplantation. Azathioprine doses range from 50 to 150 mg daily. MMF is usually prescribed at 1500 mg twice daily, although dose reductions may be necessary because of gastrointestinal upset or leukopenia. Though not standardized, trough levels of mycophenolic acid are often checked with a goal level of greater than 1.5 μg/mL.

Side effects The major side effect of azathioprine is myelosuppression. Furthermore, azathioprine should not be prescribed with allopurinol because allopurinol inhibits xanthine oxidase, leading to increased accumulation of 6-mercaptopurine, a metabolite of azathioprine, and a greater chance of myelosuppression. Major side effects of MMF include nausea, vomiting, and diarrhea, which usually respond to a decrease in dosage[8] or a switch to a sustained-release preparation.[13]

Proliferation signal inhibitors

Mechanism of action There are 2 PSIs, sirolimus and everolimus, although only sirolimus has been approved by the US Food and Drug Administration for use in heart transplant recipients, and everolimus is approved for patients after kidney and liver transplantation. These agents inhibit a kinase, target of rapamycin (see **Fig. 3**), ultimately inhibiting proliferation of T and B lymphocytes, smooth muscle cells, and endothelial cells.

Clinical trials In de novo transplant recipients, compared with azathioprine, sirolimus demonstrated less rejection and less cardiac allograft vasculopathy as measured by intravascular ultrasonography in the first 2 years.[14] However, de novo patients receiving sirolimus were more likely to develop renal dysfunction, pneumonia, and impaired wound healing, and were less likely to develop cytomegalovirus (CMV) infection. Similarly, when everolimus was compared with azathioprine and mycophenolate in de novo heart transplant recipients, there was less rejection, cardiac allograft vasculopathy, and viral infections, but worsening renal function and a higher incidence of bacterial infections.[15,16] Furthermore, high-dose everolimus (3.0 mg daily) was associated with increased mortality, and this arm was prematurely terminated. Low-dose everolimus (1.5 mg daily) was not associated with higher mortality.[16]

Administration Based on the results of the aforementioned trials, sirolimus and everolimus are rarely started de novo after heart transplantation. In the authors' institution, sirolimus or everolimus is substituted for MMF in patients with rejection, cardiac allograft vasculopathy, neoplasm, and viral infections such as CMV. PSIs may also be used in place of a calcineurin inhibitor to ameliorate renal dysfunction.[5,17]

Side effects The major side effects of PSIs include hypertriglyceridemia, myelosuppression, fluid retention, diarrhea, fatigue, and oral ulcers. Some of these side effects respond to a reduction in dose, although many patients do not tolerate PSIs because of their adverse effects.

LONG-TERM COMPLICATIONS

Rejection

Diagnosis

Transplant rejection remains one of the major causes of death after heart transplantation.[18] Rejection is most frequent during the first month after heart transplantation and declines thereafter. Because clinical symptoms of rejection are often vague, routine testing for rejection in the absence of symptoms is standard practice. Unlike renal or liver transplantation, there are no laboratory markers for rejection in heart transplantation and, thus, the endomyocardial biopsy is the standard approach for the routine surveillance of rejection. Endomyocardial biopsy is most commonly performed in an outpatient setting via a right internal jugular venous approach under fluoroscopic guidance. The most serious complications (which occur in 0.5% of cases) include tricuspid valve injury and cardiac perforation, which can result in tamponade.[19,20] Although the timing of biopsies varies from center to center, in general biopsies are performed frequently early after transplantation and less frequently as time goes on. At the authors' center, after year 1, biopsies are performed only if the heart transplant recipient develops symptoms or signs of rejection.

The purpose of the endomyocardial biopsy is to assess for myocardial damage in the form of cellular or antibody-mediated rejection. The diagnosis of cellular rejection is made in accordance with the revised International Society for Heart and Lung Transplantation (ISHLT) grading scale,

published in 2005, which simplifies the prior 1990 classification.[21,22] Biopsies are classified as: Grade 0 R, no rejection (no change from 1990); Grade 1 R, mild rejection (1990 Grades 1A, 1B, and 2); Grade 2 R, moderate rejection (1990 Grade 3A); and Grade 3 R, severe rejection (1990 Grades 3B and 4). Grade 2 R or higher rejection on biopsy is considered significant and meriting of treatment, as discussed in further detail in the next section.

The diagnosis of antibody-mediated rejection is less straightforward, but has achieved greater standardization after a consensus conference in 2010.[23] By the proposed classification, endomyocardial biopsies are graded based on the presence of histologic and immunologic findings consistent with antibody-mediated rejection (Fig. 4). Histologic findings include endothelial activation with intravascular macrophages and capillary destruction. Immunologic findings encompass complement and human leukocyte antigen (HLA) deposition.

Though not required for the diagnosis of antibody-mediated rejection, the authors also perform screening for anti-HLA antibodies post-transplantation. Antibodies are checked at months 1, 3, 6, and 12 after transplantation and then annually. The presence of high levels of donor-specific anti-HLA antibodies (usually median fluorescent intensity >10,000 or standard fluorescent intensity >200,000) is considered potentially cytotoxic and may merit a change in treatment, depending on the clinical situation.

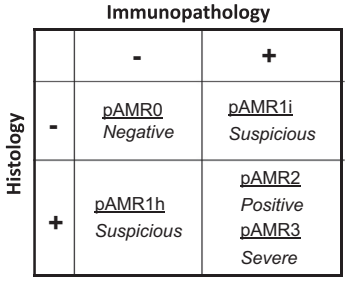

Fig. 4. Histologic findings include endothelial activation with intravascular macrophages and capillary destruction. Immunologic findings encompass complement and human leukocyte antigen deposition. The grading scheme stratifies biopsies based on: no histologic or immunologic evidence of antibody-mediated rejection (negative, pAMR0); either histologic or immunologic evidence of antibody-mediated rejection (suspicious, pAMR1h or pARM1i, respectively); both histologic and immunologic evidence of antibody-mediated rejection (positive, pAMR2); and a final category for severe findings of myocardial destruction, pAMR3. (*From* Kittleson MM, Kobashigawa JA. Antibody-mediated rejection. Curr Opin Organ Transplant 2012;17(5):554; with permission.)

Although performing an endomyocardial biopsy is straightforward, the morbidity associated with this invasive procedure has led to attempts to identify other means of diagnosing rejection. The Allomap, an 11-gene expression signature derived from peripheral blood mononuclear cells, may predict cellular rejection.[24] In a clinical trial in patients more than 6 months posttransplant, the Allomap gene-expression profile was noninferior to biopsy in the diagnosis of cellular rejection.[25] However, the Allomap has not yet been widely incorporated into clinical practice, mainly because of concerns with the randomized trial protocol, the low event rate in the clinical trial, and limitations of its generalized use.[26,27] A recent randomized controlled trial of the Allomap in the first 6 months after transplantation has also demonstrated noninferiority to the biopsy.[28] However, problems with the Allomap test include the inability to detect antibody-mediated rejection, and the fact that this test cannot be used within the first 55 days after transplant and cannot be used in patients who have received blood transfusions or hematopoietic growth factors affecting leukocytes (such as granulocyte-colony stimulating factor) within the past 30 days.[24] Thus, the widespread use of Allomap instead of endomyocardial biopsy will likely require further clinical use and experience before adoption by most transplant centers.

Treatment

The management of rejection proceeds in a stepwise fashion, based on the severity of rejection detected on biopsy and the patient's presentation (Fig. 5). Rejection most often occurs early after transplantation, and treatment is similar regardless of the timing of presentation. Grade 1 R cellular rejection or findings suspicious for antibody-mediated rejection (AMR1) in the absence of clinical or hemodynamic compromise generally merits no intervention. The management of AMR1 is controversial at present, and at some centers treatment may proceed as for higher levels of rejection, as described next.

More serious findings on the biopsy, including Grade 2 R or higher cellular rejection, or higher antibody-mediated rejection (AMR2), require treatment. The intensity of treatment depends on the patient's presentation. If the patient has no symptoms of heart failure and normal left ventricular ejection fraction, treatment options include oral or intravenous pulse steroids, targeting higher levels of immunosuppressive medications, switching from cyclosporine to tacrolimus,[9,10] or switching from MMF to a PSI.[14,15,29] Given the equivalent success of intravenous and oral corticosteroid therapy for the treatment of

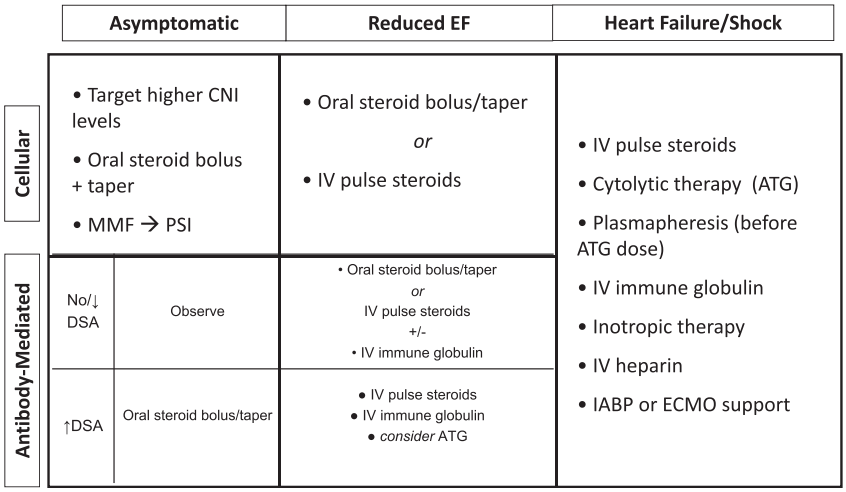

Fig. 5. Treatment of rejection. Treatment proceeds in a stepwise fashion based on the severity of rejection detected on biopsy and the patient's presentation. ATG, antithymocyte globulin; CNI, calcineurin inhibitor; DSA, donor-specific antibodies; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon counterpulsation; IV, intravenous; MMF, mycophenolate mofetil; PSI, proliferation signal inhibitor.

asymptomatic cellular rejection,[30] an outpatient course of oral corticosteroids is often the first-line treatment for asymptomatic cellular rejection. Asymptomatic antibody-mediated rejection is more challenging. Recent studies indicate that it may be associated with poor outcomes,[31–33] but it is unclear whether treatment affects outcomes. At the authors' institution such patients will receive an oral corticosteroid bolus, consideration of intravenous immune globulin, and close monitoring of donor-specific HLA antibodies.

For patients with a reduced ejection fraction on echocardiogram, treatment is more aggressive. A reduction in ejection fraction in the absence of biopsy evidence for rejection may be treated with intravenous corticosteroids and cytolytic therapy with antithymocyte globulin in addition to the adjustments in immunosuppressive medications outlined earlier. If there is evidence of AMR2 or higher, such patients will also receive intravenous immune globulin. If donor-specific anti-HLA antibodies are present in the setting of antibody-mediated rejection or a decrease in ejection fraction, patients may receive a steroid bolus and taper, or more intensive therapy with intravenous immune globulin, rituximab, or bortezomib.

Finally, in patients presenting with cardiogenic shock the results of the biopsy are less important, and aggressive empiric treatment includes intravenous corticosteroids, cytolytic therapy, plasmapheresis, intravenous immune globulin, intravenous heparin (as patients often have thrombotic occlusion of the cardiac microvasculature on postmortem examination[34,35]), and hemodynamic support with intra-aortic balloon counterpulsation or even extracorporeal membrane oxygenation.[36]

The protocols for the treatment of rejection will vary between transplant centers, as there are no randomized trials comparing strategies. However, given the relatively small number of heart transplants performed internationally and the relative rarity of rejection, such trials would be difficult to conduct or power to assess differences between treatment strategies. Thus, as a clinician, one must rely on experience and judgment to formulate the treatment plan that maximizes benefit and minimizes toxicity of these therapies.

Long-term management

Whereas cellular rejection is often successfully treated with corticosteroids and cytolytic therapy, resulting in a resolution of heart failure and normalization of the ejection fraction,[37] management of antibody-mediated rejection is often more complicated. Patients often have a persistent reduction in ejection fraction, restrictive physiology leading to recurrent symptoms of heart failure, and accelerated progression of transplant coronary artery disease.[37]

The management of such patients with a persistent drop in ejection fraction after treatment of symptomatic rejection is not well established (**Fig. 6**). The authors often rely on therapies to reduce the levels of donor-specific anti-HLA antibodies, including rituximab and bortezomib, as well as photopheresis to alter the function of T cells. In small case series, such therapies have

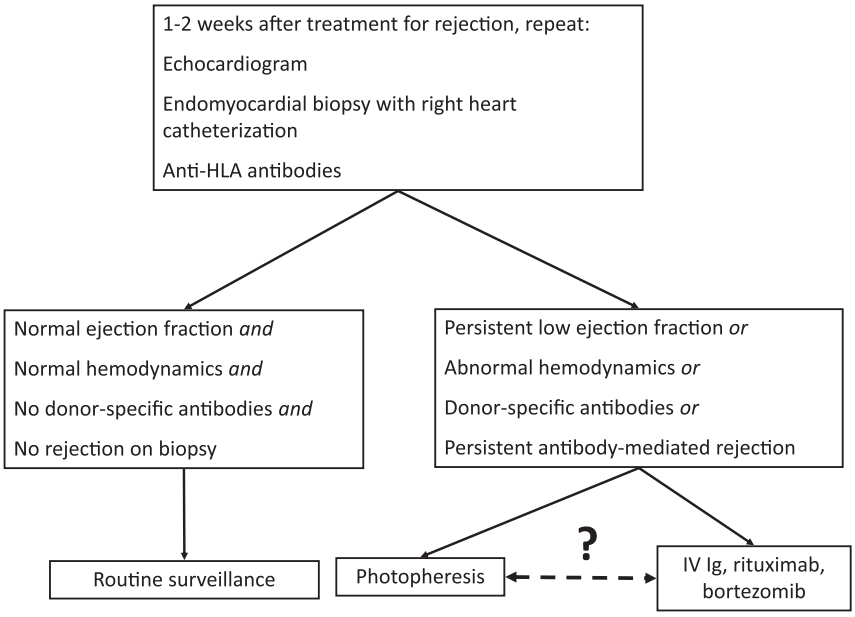

Fig. 6. Long-term management of antibody-mediated rejection. After treatment of antibody-mediated rejection, patients may have a persistent reduction in ejection fraction, restrictive physiology leading to recurrent symptoms of heart failure, and accelerated progression of transplant coronary artery disease. The management of such patients with a persistent drop in ejection fraction after treatment of symptomatic rejection is not well established. The authors often rely on rituximab, bortezomib, or photopheresis. The choice between rituximab, bortezomib, and photopheresis is not well established, and is often decided on a case-by-case basis. Ig, immunoglobulin. (*From* Kittleson MM, Kobashigawa JA. Antibody-mediated rejection. Curr Opin Organ Transplant 2012;17(5):556; with permission.)

shown benefit,[38,39] although often such patients go on to require redo transplantation.

Cardiac Allograft Vasculopathy

Incidence and prognosis

The incidence of cardiac allograft vasculopathy (CAV) varies widely, owing to differences in the definition of disease and patient populations. In one of the largest cohorts studied, of more than 6000 angiograms performed in more than 2600 patients from 39 institutions, angiographically significant CAV was noted in 42% of the patients at 5 years.[40] In a more recent study, although only 10% of heart transplant recipients developed CAV at 5 years there was a substantial increase in incidence thereafter, with 50% having developed disease by 10 years.[41] CAV can occur as soon as 1 year after transplantation, and this early disease is more aggressive and is associated with a worse prognosis.[42] In one study, those with angiographic disease had a 3.4-fold increased risk of major cardiac events and a 4.6-fold increase risk of death over a 3.5-year follow-up.[43] In patients without apparent angiographic epicardial disease, microvascular abnormalities may be present, and are associated with adverse outcomes.[44]

Clinical presentation

Given the denervation of the transplanted heart, patients do not experience typical angina, and the presentation of CAV differs from that of nontransplant CAV, as outlined in **Table 3**.[45] However,

Table 3
Features distinguishing cardiac allograft vasculopathy from nontransplant atherosclerosis

Nontransplant Atherosclerosis	Cardiac Allograft Vasculopathy
Most epicardial disease	Panvascular disease (including microvasculature)
Slow progression	Rapid progression
Eccentric lesions	Concentric lesions (generally)
Lipid rich	Generally lipid poor
Early calcification	Late calcification
Compensatory remodeling with early dilation (Glagov phenomenon)	Arterial constriction

over time patients may develop cardiac reinnervation, and chest pain caused by ischemia and infarction in transplant patients has been documented.[46–48] Electrocardiographic changes with myocardial infarction may be atypical, owing to baseline abnormalities or heterogeneous disease resulting from diffuse vasculopathy.[49] In general, the atypical presentation often leads to lower utilization of revascularization therapies and, consequently, worse outcomes,[43,49] including heart failure, arrhythmia, or sudden death. For this reason, routine surveillance angiography is performed in cardiac transplant recipients, usually at 1-year intervals.

Detecting cardiac allograft vasculopathy

CAV is usually beyond therapeutic intervention by the time symptoms develop, so surveillance is essential to monitoring the development of CAV. Coronary angiography remains the mainstay of CAV detection, although it has limitations. Coronary angiography relies on the ability to compare normal segments of the vessel with diseased segments. The diffuse nature of CAV often results in underestimation of disease because there is no reference segment whereby the normal diameter of the vessel can be assessed. Comparison with prior studies may help, but requires the use of the same angiographic protocol at each study to avoid confounding by technical factors such as angiographic projections and magnification.

Intravascular ultrasonography (IVUS) is currently the only technique offering cross-sectional images of the coronary vessel wall comparable with histologic sections (**Fig. 7**). Intimal area can be quantitatively assessed to detect even early plaque burden. Sequential images are usually obtained as the catheter is pulled back to determine the extent of the disease along a vessel wall. In several studies, IVUS is more sensitive than angiography in detecting CAV.[50–53] IVUS also has prognostic value: progression of intimal thickening greater than 0.5 mm in the first year after heart transplantation is associated with an increased risk of death and development of angiographic CAV up to 5 years after transplantation.[42] Nevertheless, IVUS has several limitations: it is highly invasive, requires anticoagulation and the use of expensive single-use catheters, and its evaluation is mainly limited to the major epicardial vessels.

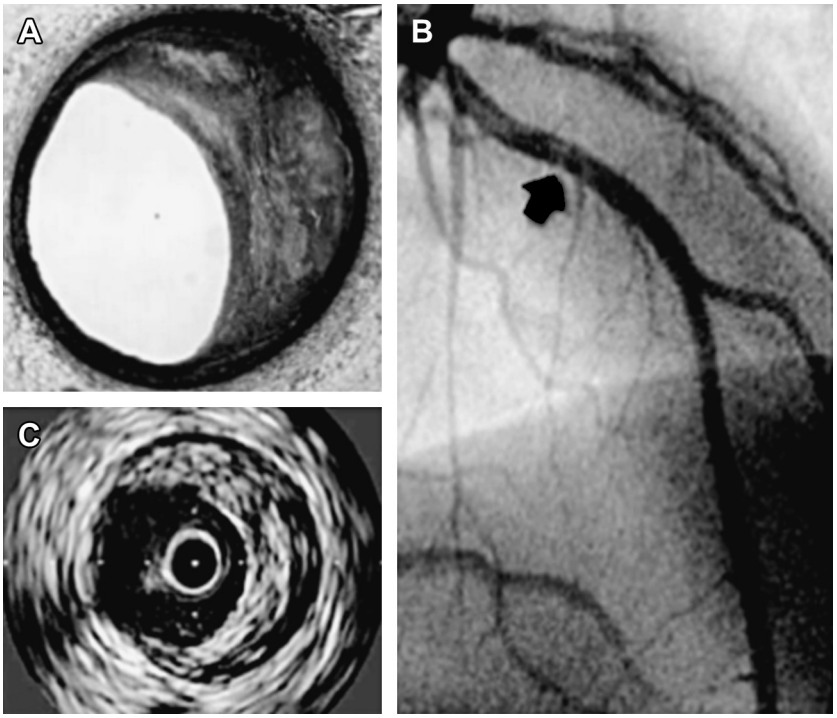

Fig. 7. Concentric or eccentric subintimal proliferation in cardiac allograft vasculopathy seen histologically (*A*) are underestimated in lesion severity angiographically (*B*, *arrow*), but are better appreciated by intravascular ultrasonography (*C*). (*From* Patel JK, Kobashigawa JA. Cardiac allograft vasculopathy. In: Ahsan N, editor. Chronic allograft failure: natural history, pathogenesis, diagnosis and management. Austin (TX): Landes Bioscience; 2008; with permission.)

Treatment of cardiac allograft vasculopathy

Clinically apparent CAV is associated with a poor prognosis, so prevention is an important strategy (**Box 2**). Agents used in the treatment and prevention of conventional atherosclerosis are used for CAV. Aspirin is given, because of its established role in nontransplant coronary disease. Control of hypertension and hyperlipidemia is paramount. 3-Hydoxy-3-methyl-glutaryl coenzyme A reductase inhibitors are particularly important, as they also prevent allograft rejection.[54] The PSIs also show significant promise in reducing the progression of intimal thickening by IVUS.[14–16]

Once clinically significant CAV is apparent, percutaneous coronary intervention (PCI) is successful for focal disease, although restenosis is common in the transplant setting.[55] Drug-eluting stents may help, but restenosis rates continue to be higher than for similar interventions in the nontransplant population.[56,57] There is no evidence to date that PCI alters the prognosis of CAV and, because many patients with significant disease are asymptomatic, intervention often presents a dilemma. Patients with multivessel focal disease with adequate distal target vessels may be candidates for surgical revascularization with coronary artery bypass grafting (CABG). Efficacy is difficult to determine as relatively small numbers have been reported, reflecting the many patients who do not have adequate targets and the preferential use of PCI.

Box 2
Treatment options for cardiac allograft vasculopathy

Prevention
- Aspirin
- Control of hypertension (calcium-channel blockers, angiotensin-converting enzyme inhibitors)
- Hydroxymethylglutaryl coenzyme A reductase inhibitors
- Control of diabetes
- Mycophenolate mofetil
- Proliferation signal inhibitors (sirolimus, everolimus)

Treatment
- Drug-eluting stents
- Proliferation signal inhibitors
- Surgical revascularization
- Retransplantation

Retransplantation may be a consideration for many patients with advanced CAV who are not amenable to PCI or CABG. After retransplantation, patients have survival comparable with that of patients undergoing a first transplant, with no increased incidence of CAV in the second donor heart.[58] The scarcity of donor hearts, however, creates an ethical dilemma. Some argue that it is better to maximally distribute organs rather than to allocate 2 organs to the same individual. Others contend that patients needing a second transplant should be considered on the same basis as those being evaluated for a first transplant.

Infection

Because of immunosuppressive therapy, cardiac transplant recipients are at risk for infection in a generally predictable pattern based on time after transplantation.[59] A summary of the infection risk is provided in **Fig. 8**, and antimicrobial prophylaxis is summarized in **Table 4**.

As with acute rejection, monitoring for immune status and infection risk remains problematic. This problem has led to several attempts to investigate monitoring assays, none of which are well validated at present, and there is currently no standard approach to accurately assess the risk for infection in a transplant recipient. However, an immune-monitoring assay (ImmuKnow; Cylex, Columbia, MD) performed on peripheral blood, which measures adenosine triphosphate (ATP) release from activated lymphocytes, may offer some guidance in profoundly immunosuppressed patients.[60,61] In the largest study to date in heart transplant recipients, the average T-cell immune function (TCIF) score was significantly lower in patients who developed an episode of infection within 1 month after the measurement, compared with steady-state patients.[62] A TCIF score of less than 200 ng ATP/mL was associated with future infection. The authors have used this information to tailor immunosuppression. In a patient with infection, if the TCIF score is less than 200 ng ATP/mL, immunosuppression will be reduced either by decreasing the dose of MMF or by targeting lower drug levels of the calcineurin inhibitor or PSI. If the TCIF score is 200 to 500 ng ATP/mL, the patient has an adequate level of immunosuppression. If the TCIF score is greater than 500 ng ATP/mL, the patient may be under-immunosuppressed and the MMF dose may be increased, or high drug levels of the calcineurin inhibitor or PSI may be targeted.

Malignancy

Malignancy is one of the most common causes of mortality in heart transplant recipients.[18] The

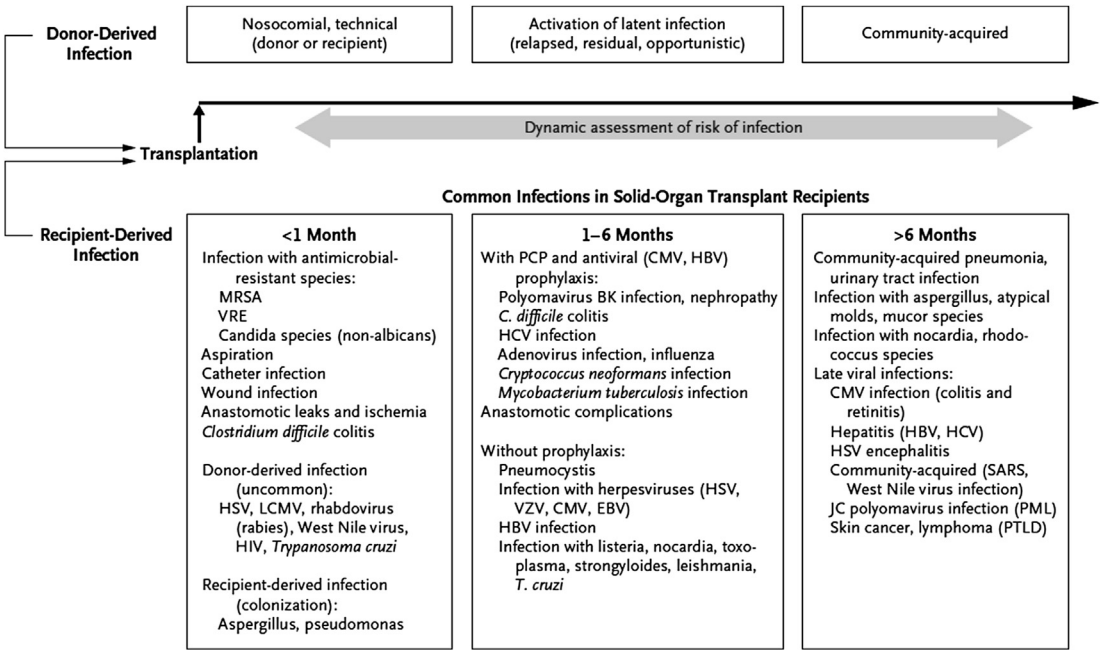

Fig. 8. Changing timeline of infection after organ transplantation. Infections occur in a generally predictable pattern after solid-organ transplantation. The development of infection is delayed by prophylaxis and is accelerated by intensified immunosuppression, toxic drug effects that may cause leukopenia, 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. (*Reproduced from* Fishman JA. Infection in solid-organ transplant recipients. N Engl J Med 2007;357(25):2606; with permission.)

ISHLT registry demonstrates that cumulative risk of malignancy is 26% by 8 years, mostly (18%) attributable to skin cancer.[18] A detailed discussion of posttransplant malignancy is beyond the scope of this review. However, the most critical point of treatment of malignancies is prevention. The authors encourage all heart transplant recipients at their institution to undergo routine health

Table 4
Recommended antimicrobial prophylaxis after heart transplantation

Infection	Antimicrobial	Duration
Toxoplasmosis *Pneumocystis* pneumonia	Trimethoprim/sulfamethoxazole Atovaquone or Dapsone if allergic to sulfa drugs	1 y
Cytomegalovirus	Valganciclovir	CMV IgG donor (D)/CMV IgG recipient (R) status: D−/R−: 3 mo (consider acyclovir, a less expensive alternative, for such low-risk patients) D−/R+: 6 mo D+/R+: 6 mo D+/R−: 12 mo
Oral candidiasis	Clotrimoxazole	3 mo

Abbreviations: CMV, cytomegalovirus; IgG, immunoglobulin G.

Table 5
Drug-drug interactions

Drugs that Increase Cyclosporine/ Tacrolimus Levels	Drugs that Decrease Cyclosporine/Tacrolimus Levels	Drugs that Enhance Nephrotoxicity
Cyclosporine		
Calcium-channel blockers: diltiazem, verapamil, nifedipine, nicardipine Antibiotics: erythromycin, clarithromycin, doxycycline Antifungal: ketoconazole, voriconazole Gastrointestinal (GI) agents: Metoclopramide Miscellaneous: amiodarone, allopurinol, grapefruit, grapefruit juice	Antibiotics: nafcillin and rifampin Anticonvulsants: phenytoin, phenobarbital, and carbamazepine Miscellaneous: hypericum perforatum, ticlopidine, cholestyramine	Antibiotics: gentamicin, tobramycin, vancomycin, trimethoprim/ sulfamethoxazole Nonsteroidal anti-inflammatory drugs: all formulations, colchicine Antivirals: acyclovir GI agents: cimetidine, ranitidine
Tacrolimus		
Calcium-channel blockers: diltiazem, verapamil, nifedipine, nicardipine Antibiotics: erythromycin, clarithromycin Antifungal: ketoconazole, voriconazole, fluconazole GI agents: metoclopramide, cimetidine, omeprazole HIV protease inhibitors Miscellaneous: methylprednisolone, grapefruit, grapefruit juice	Antibiotics: rifampin Anticonvulsants: phenytoin, phenobarbital, carbamazepine Miscellaneous: hypericum perforatum, cholestyramine	Antibiotics: aminoglycosides Antifungals: amphotericin B Antineoplastics: cisplatin Cyclosporine

Adapted from Kansara P, Kobashigawa JA. Management of heart transplant recipients: reference for primary care physicians. Postgrad Med 2012;124:219. Copyright © 2012, with permission from JTE Multimedia.

maintenance screenings with their primary care physicians. In addition, patients are instructed to use sun protection and to establish care with a dermatologist for routine skin examinations. The initial approach to malignancy is reduction of immunosuppression, and switching patients with newly diagnosed malignancy to a PSI such as sirolimus or everolimus instead of a calcineurin inhibitor or MMF, because of the possible protective effect of PSIs in malignancies.[63–65]

General Medical Management

It is essential that all heart transplant recipients receive regular care from an internist for routine health maintenance. Such patients require the same general medical surveillance as nontransplant patients, including age-appropriate cancer screening for malignancies of the cervix, breast, colon, and prostate. Internists may also manage the long-term complications of heart transplant recipients, including renal dysfunction, hypertension, dyslipidemia, diabetes, osteoporosis, and gout. However, it is essential to instruct transplant recipients to inform the transplant center of any new medication recommended by the internist, as there may be unforeseen interactions that should be monitored (Table 5).

SUMMARY

Over the last 4 decades, cardiac transplantation has become the preferred therapy for select patients with end-stage heart disease. Improvements in immunosuppression and posttransplant care have resulted in a substantial decrease in acute allograft rejection, which previously led to significantly limited survival of transplant recipients. However, major impediments to long-term allograft survival exist, including rejection, infection, CAV, and malignancy. Nevertheless, through careful balance of immunosuppressive therapy and vigilant surveillance for complications, further advances in the long-term outcomes of heart transplant recipients are expected over the decades to come.

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