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Complications After Heart Transplantation in Adults: an Update

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Abstract
Purpose of Review The goal of this review article is to highlight our understanding of potential complications after heart transplantation. We aim to discuss recent advances within the field that directly impact the management of heart transplant recipients. Our target audiences include cardiologists, emergency medicine, and internal medicine providers.
Recent Findings Heart transplantation remains definitive therapy for end-stage heart failure. Complications after transplant can be divided in to post-operative, early, and late. Complications are related to the differing physiology of the denervated transplant heart as well as the immunosuppressive medications necessitated to maintain graft function. These include primary graft dysfunction, allograft rejection, chronic renal insufficiency, cardiac allograft vasculopathy, and malignancy.
Summary The anticipation and management of complications in patients after receiving a heart transplant involve a comprehensive understanding of the differences in the transplanted heart and effects of immunosuppressive therapies.

Keywords Heart transplant · Complications · Rejection · Infection · Graft failure

Abbreviations
(HLA) human leukocyte antigen
(PGD) primary graft dysfunction
(MCS) mechanical circulatory support
(CAV) cardiac allograft vasculopathy

Introduction

Heart transplantation remains the definitive therapy for end-stage heart failure. In the USA, the annual number of heart transplants performed has been increasing over the past decade. However, the number of potential donor hearts available has been constant while the number of active candidates on the transplant waiting list has been increasing [1]. Furthermore, the medical complexity of heart transplant recipients has been increasing over time. There are a growing number of older transplant recipients, a rise in the use of mechanical circulatory support (MCS), and patients with greater levels of detectable antibodies prior to transplant [2–3,4•]. This evolving landscape has placed heart transplant recipients at an increased risk for adverse outcomes [5]. In this review, we will discuss the prevalence, pathophysiology, and management of complications after heart transplantation in adults. Furthermore, we will briefly review medical chief complaints and evaluation consideration in heart transplant patients.

Methodology

We selected PubMed and Google Scholar as our databases. We searched for articles published over the past 5 years. We searched for the following keywords from 2014 to 2019: "heart transplantation," "heart transplant complications," "heart transplant and infections," "heart transplant rejection," "primary graft dysfunction," and "heart transplant and malignancy." The window of time for search was expanded if no recent articles were found.

The Transplanted Heart

For the practitioner providing care to a heart transplant recipient, it is important to be aware of the changes in cardiac physiology which occur after transplant. The transplanted heart is unlike the native heart due to the absence of efferent

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and afferent nerve innervation with the departure of neural input to the sinoatrial node [6]. This occurs as a result of surgical dissection to the post-ganglionic neurons. The resting basal heart rate of the transplanted heart is elevated (average 95 beats per minute) due to the absence of parasympathetic innervation. The lack of direct sensory input decreases the ability of patients to experience symptomatic angina. Rarely, instances of structural sympathetic reinnervation after transplantation has occurred [7]. The frequency and sum of either parasympathetic or sympathetic reinnervation which occurs per patient are highly variable. The presence of reinnervation may increase the ability to feel angina from myocardial ischemia as well as improve ventricular response to exercise.

The conduction system of the transplanted heart is also different than native heart due to surgical technique and ischemia-reperfusion injury. As a result of physiologic differences of the transplanted heart, select cardiac medications have variable effects. Beta-blockers early after transplantation can decrease exercise capacity and ejection fraction due to inability to increase heart rate in response to physiologic needs [8]. Atropine, an anticholinergic drug used to treat bradyarrhythmias via inhibition of vagus nerve, has little effect on the heart rate of the denervated, transplanted, heart [9, 10••]. Conversely, adenosine which binds type-1 adenosine (A_1) receptors in the treatment of supraventricular tachycardia has increased sensitivity in the transplanted heart. Therefore, a dose reduction is recommended prior to its use [10••, 11].

Post-Operative Complications

Complications after heart transplantation can be divided in terms of timing: post-operative, early, and late [12]. The post-operative monitoring early after transplantation should be done with the assistance of hemodynamic monitoring (i.e., arterial line, continuous telemetry, and Swan ganz catheter monitoring), imaging (intraoperative transesophageal echocardiography), and use of vasopressor and inotropic support agents as indicated. Typically, the transplanted heart has minimal catecholamine stores and exogenous supplementation is necessary for the early intensive care unit (ICU) course. Specific regimens utilized to support the newly transplanted heart are variable by transplant center. Post-operative cases of profound hemodynamic instability should be investigated for the following causes.

Hyperacute rejection is a rare, post-operative complication which can occur shortly after transplantation. The incidence of hyperacute rejection has decreased over time [4•]. The process occurs when preformed antibodies to the allograft attack by binding to HLA and non-HLA antigens [13]. Hyperacute rejection is managed often in the operating room setting with inotropic/mechanical support and aggressive immunosuppression, including corticosteroids, anti-thymocyte globulin, plasmapheresis, and intravenous immunoglobulin (IVIG) [14].

Cardiac tamponade is another post-operative complication which typically presents within the first days with hemodynamic instability including rising right-sided filling pressures and decreased cardiac output. Pericardial effusion visualization after heart transplantation is not infrequent, with incidences ranging from 10 to 20% [15, 16] after heart transplant. Therefore, particular assessment to ensure hemodynamic contribution exists from an effusion is important [17]. Evaluation is typically performed with either transthoracic or transesophageal echocardiogram. Management is surgical exploration with evacuation if occurring in the immediate post-operative period [14].

Primary graft dysfunction (PGD) is the development of either left, right, or biventricular dysfunction within 24 h of transplant with no identifiable cause [18]. Risk assessment prior to transplant is advised; factors including ischemic time, African American recipient, and amiodarone treatment prior to transplant are known to be associated with the development of PGD [18]. PGD can be categorized by severity (mild/moderate/severe) and also as left or right sided. Importantly, the criteria to classify PGD include imaging (echocardiography) and hemodynamic findings [19••]. The management of PGD is an area of active investigation, but currently limited to inotropes or mechanical circulatory support (MCS) to provide support and, in rare cases, re-transplantation.

Early Complications

Beyond post-operative complications, there are specific early complications that can occur after transplantation. The development of right ventricular (RV) dysfunction is a meaningful finding associated with increased mortality [10••]. Elevated pulmonary vascular resistance prior to transplant that is not reversible is a risk for the development of the new right ventricle to have dysfunction after transplant [20]. The evaluation of RV relies upon imaging and hemodynamic assessment. The management of RV failure after transplant includes optimization of preload, inotrope/vasopressor support, ventilatory support, and maintenance of sinus rhythm [21].

Dysrhythmias after heart transplant are a commonly seen entity, with sinus node dysfunction having a prevalence as high as 50% [22]. Sinus bradycardia is often seen in patients who were prescribed amiodarone prior to transplantation given the long half-life of the medication. Bradycardia is often managed with chronotropic agents such as terbutaline or isoproterenol as guidelines-recommend maintenance of a heart rate of 90 beats per minute [10••]. Up to 10% of patients require a permanent pacemaker for persistent, symptomatic bradycardia [23]. Atrial and ventricular arrhythmias after

transplantation are less frequently observed as compared to sinus bradycardia. Atrial fibrillation is often associated with acute rejection or (later on) with the development of cardiac allograft vasculopathy (CAV) of the transplanted heart [24]. Atrial flutter is less often associated with allograft rejection [24]. Ventricular arrhythmias after transplant are often seen early post-operatively and not necessarily associated with rejection, but likely the result of ischemia-reperfusion injury. The management of tachyarrhythmias after transplantation is typically performed by rate control to 90–100 bpm with class II–IV anti-arrhythmic agents.

Acute rejection of the transplanted heart is a major complication that has had a decreased incidence over time as our understanding of immunosuppression has improved. Data from the International Society of Heart and Lung Transplantation (ISHLT) demonstrates a 22% incidence of graft rejection leading to hospital admission within 1 year of transplant between 2005 and 2010. Between 1994 and 1999, the incidence was significantly greater (42%) [25]. Risk factors of the recipient for allograft rejection include young age, black race, and female sex [26]. Heart transplant recipients with acute rejection are often asymptomatic; however, when symptoms are present, they typically are related to decompensated heart failure including shortness of breath, orthopnea, edema, and fatigue [27]. Additionally, patients can present with low-grade fevers, dizziness, or symptoms related to arrhythmias. Diagnostic testing for suspected cases of rejection should include an electrocardiogram (ECG) and echocardiography which can demonstrate systolic and diastolic abnormalities. More recently, cardiac MRI (CMR) has shown promise in the evaluation of suspected rejection; T2 mapping and basal extracellular volume measurement can provide excellent sensitivity for the diagnosis of both cellular- and humoral-mediated rejection [28]. Other tools to evaluate cases of suspected rejection include the use of cardiac biomarkers. Cardiac troponin and natriuretic peptides provide insight into myocardial injury as well as hemodynamic wall stress. However, serum measurement in the evaluation of allograft rejection has limited utility given the lack of specificity [29–31]. Ultimately, the detection and grading of allograft rejection rely upon the endomyocardial biopsy (EMB). The procedure itself is associated with a low rate of complications, which includes transient right bundle branch block, tricuspid regurgitation, hematoma, and rarely, right ventricular perforation [32]. Rejection is most commonly due to acute cellular rejection (ACR), through T cell–mediated mechanisms. ACR typically occurs within the first 6 months of transplant and is graded on a scale from mild to severe [33]. Antibody-mediated rejection (AMR) has more recently been recognized as a unique entity with a 2013 working group development of a grading scale from 1 to 3 [34]. AMR manifests in up to 15% of heart transplant recipients, and the diagnosis of AMR is contingent upon combined histologic and immunopathologic review of EMB. There are also instances of biopsy-negative rejection in which there is evidence of graft dysfunction and normal EMB. This may be related to sampling from the EMB itself. Novel methods to enhance our ability to detect graft rejection under investigation include gene expression profiling, cell-free DNA detection, and microarray technology [35–37]. The management of graft rejection is dictated by severity and acuity of presentation. Specifically, grade 2R and/or AMR2 (or greater) warrant administration of immunosuppressive therapies. Asymptomatic patients are often treated with oral steroids while symptomatic patients can be managed with therapies including intravenous steroids, higher doses of immunosuppression, and anti-thymocyte globulin (ATG). Patients presenting with cardiogenic shock often require therapies which include plasmapheresis, IVIG, heparin, and hemodynamic support (i.e., intra-aortic balloon pump or extracorporeal membrane oxygenation (ECMO)) [38]. Continuous administration of intravenous heparin should be considered in these cases and autopsy studies have demonstrated microvascular thrombi.

Both opportunistic infections and reactivation of latent infections remain a common complication after heart transplantation. The net state of immunosuppression in transplant recipients is affected by multiple factors including immunosuppressive therapies, underlying immune deficiencies, metabolic conditions, and malnutrition [39]. The greatest risk for infection as a cause of death occurs after the first month of transplant and remains through the first year [25]. The type of infection is often related to time after transplant. Typically, nosocomial infections occur during the first month while opportunistic and community-acquired infections occur after this time period [39]. The presence of MCS as a "bridge" to transplant is associated with a higher risk of post-transplant infectious complications [40]. Bacterial infections are the most common early infectious cause of morbidity, with *Staphylococcus aureus* being the most common pathogen [41, 42]. Staphylococcus infections typically manifest as wound infection, pneumonia, line-associated, or a urinary tract infection. Candidiasis is the most common invasive fungal infection. Candidiasis can present as a mucosal surface infection (i.e., oral, esophageal, sternal wound) or disseminated infection. Cytomegalovirus (CMV) is a commonly found virus in the organ donor population, and it is known that CMV-positive donor hearts can be transplanted into CMV-negative recipients [43]. CMV infection after transplant commonly occurs within the first 2 months of transplant and is associated with the long-term development of CAV [44]. Infections often present as CMV syndrome, with fevers, chills, and malaise. CMV can also progress to invasive disease including pneumonitis, hepatitis, and cholecystitis.

The evaluation of possible infection in a heart transplant recipient should include both donor and recipient history of infection, exposure history, and current immunosuppressive

regimen intake. The treatment of infectious complications after heart transplant includes targeted antimicrobial therapies, possible dose reduction of immunosuppression, and risk reduction for future exposure. Management should include consultation with a transplant infectious disease specialist. Additionally, the ImmuKnow assay (Cylex) is a tool that detects cell-mediated global immunity [45]. Multiple small studies have been performed utilizing this test in heart transplant recipients, with one meta-analysis concluding ATP values of 130 ng/mL or less are associated with an increased risk for infection. Thus, this tool may help transplant physicians make adjustments to immunosuppressive regimens based on risk stratification for future infections [46].

Late Complications

The median survival for adults after heart transplantation is 11 years [5]. Cardiac allograft vasculopathy (CAV) is a form of chronic rejection of the transplanted heart and major cause of late morbidity and mortality. CAV is due to a pan-arteritis with concentric, longitudinal intimal thickening of the epicardial coronary arteries, and likely the microvascular arteries as well [47]. The development of CAV is caused by inflammatory cells as well as the development of atherosclerotic deposition within the coronary arterial intima. Risk factors for CAV development include donor age, diabetes mellitus, hypertension, hyperlipidemia and recipient age, and HLA match. Due to the lack of innervation to the transplanted heart, patients who develop severe CAV typically present late with silent myocardial infarction, graft dysfunction, or sudden death. The detection of CAV is reliant upon invasive coronary angiography with intravascular ultrasound to improve sensitivity of detection [48, 49]. Advanced imaging including coronary computed tomography angiography (CCTA) and positron emission tomography–computed tomography (PET-CT) are areas of active investigation to detect sub-clinical CAV [48, 50]. The management of CAV includes risk factor reduction, use of proliferation signal inhibitors when tolerated for immunosuppression [51], and statin therapy [52]. Additionally, there is a role for invasive therapies including percutaneous coronary intervention (PCI) and bypass surgery (CABG) to help treat CAV and its sequelae.

Malignancy after heart transplant is a common late complication with a 10% risk of de novo solid malignancy between 1 and 5 years after transplant [53]. The chronic use of immunosuppression to prevent allograft rejection is integral in increasing the risk for malignancy. Skin cancer remains the most common type of cancer and there has been a slight increase in the incidence of de novo solid malignancy over time [53]. Importantly, survival in patients after the development of malignancy is significantly lower than in patients without malignancy. The management of malignancy after heart transplant is primarily with standard oncologic therapies. Adjusting immunosuppression from a regimen which includes an antimetabolite to proliferation signal inhibitor (PSI) may decrease the risk of subsequent malignancy development [54]. Moreover, patients should receive annual screening by a dermatologist and age-appropriate cancer screening after heart transplantation to ensure de novo malignancies are diagnosed early in their disease course and treated appropriately.

Renal dysfunction after heart transplant is an important long-term complication [55] and is associated with a poor prognosis [56]. Typically, the greatest loss of kidney function occurs during the first year following heart transplant. Calcineurin inhibitors (CNIs) are a mainstay of the maintenance immunosuppression after and are associated with nephrotoxicity with progressive tubule-interstitial damage and glomerulosclerosis. Therefore, close monitoring of serum drug levels is critical. The early withdrawal of CNI therapy for a proliferation signal inhibitor can improve renal function with a lower incidence of CAV, but with a higher incidence of allograft rejection [57•]. The Scandinavian Heart Transplant Everolimus De Novo Study With Early Calcineurin Inhibitors Avoidance (Schedule) trial demonstrated that a regimen of PSI, low-dose CNI, steroids, and mycophenolate mofetil (MMF) with CNI discontinuation after 7 weeks resulted in improved long-term renal function [57•]. This regimen, used selectively, may offer acceptable immunosuppressive efficacy with a sustained renal advantage. Table 1 summarizes major complications after heart transplantation and management strategies. Figure 1 demonstrates major complications after heart transplantation.

Clinical Management Issues

Shortness of Breath

In heart transplant patients presenting for acute medical care with shortness of breath, a comprehensive evaluation should be undertaken [27]. Specifically, a transplant history including date of transplant, prior episodes of rejection, prior angiograms, immunosuppression regimen (and adherence), should be sought after. Graft rejection and infection are more common early after transplant while CAV or de novo malignancy occur more frequently late [58]. Additionally, any history to suggest sepsis including fever, productive cough, or malaise should be obtained. Symptoms and signs consistent with decompensated heart failure are concerning for allograft rejection or CAV, a form of chronic rejection. Diagnostic testing should include basic labs, cardiac biomarkers, ECG, chest imaging, and urgent echocardiography to evaluate graft function. Within the first year of transplant, the ECG typically demonstrates normal sinus rhythm or sinus tachycardia [59]. More common abnormalities include right intraventricular

Table 1 Summary of complications after heart transplantation

Complication	Time after transplant	Evaluation	Management	Pearls
Hyperacute rejection	Post-operative	Hemodynamics, imaging, retrospective crossmatch	MCS, IVIG, ATG, plasmapheresis, corticosteroids.	Occasional cases in setting of negative pre-operative PRA
Tamponade	Post-operative	Transesophageal or transthoracic echocardiography	Surgical exploration	Elevated risk in setting of coagulopathy or surgical bleeding
PGD	Post-operative	Hemodynamics consistent with shock and echocardiography to confirm graft dysfunction	MCS and supportive care	Recently established universal definition to formalize diagnosis and treatment strategies
RV failure	Post-operative/early	Hemodynamic monitoring of right atrial and pulmonary arterial pressures and echocardiographic evaluation of RV	Preload optimization, inotrope-vasopressor support, maintenance of sinus rhythm, and ventilatory support	
Dysrhythmias	Early/late	ECG, holter/event monitor, implantable loop recorder	Per rhythm	Sinus bradycardia common early post-transplant and elevated resting HR afterwards
Acute rejection	Early/late	Echocardiography, biomarkers, CMR, EMB, angiography	Steroid pulse, IVIG, plasmapheresis, ATG, heparin, and MCS	Highly variable patient presentations
Infection	Early/late	Lab testing including CBC with differential, T cell assay, cultures, and imaging.	Per pathogen	Fever often absent in opportunistic infections
CAV	Late	Angiography with IVUS, CCTA, PET-CT, stress echocardiography	Risk factor reduction, statin, PSI, re-transplantation	Chest pain less common resulting from denervated heart
Malignancy	Late	Skin exam, blood testing, and imaging	Per primary	Routine surveillance skin evaluation is recommended
Renal failure	Early/late	Blood and urine testing	Avoidance of nephrotoxins, hemodialysis, kidney transplantation	Consider exchange of CNI for PSI to maintain renal function

ATG, anti-thymocyte globulin; *CMR*, cardiac magnetic resonance; *CNI*, calcineurin inhibitor; *CBC*, complete blood count; *CCTA*, coronary computed tomography angiography; *EMB*, endomyocardial biopsy; *HR*, heart rate; *IVUS*, intravascular ultrasound; *IVIG*, intravenous immunoglobulin; *MCS*, mechanical circulatory support; *PRA*, panel reactive antibodies; *PET-CT*, positron emission tomography–computed tomography; *PSI*, proliferation signal inhibitor

conduction delay or atrial enlargement. Biomarkers such as natriuretic peptides and troponin remain elevated with a progressive decline typically reaching steady state approximately 12 weeks after transplant [60]. Abnormal graft function or highly elevated biomarkers should trigger consideration of EMB as well as possibly angiography for evaluation of CAV.

Bruising

In heart transplant patients presenting with signs of bruising, medications including herbal supplements and immunosuppressive regimen (with consideration to recent adjustments) should be evaluated. Labs measured should include serum hemoglobin, platelet count, and coagulation variables. Medications such as corticosteroids and aspirin can predispose to easy bruising. Withdrawal of steroids can be considered in some cases based on the Tacrolimus in Combination, Tacrolimus Alone Compared (TICTAC) trial, which demonstrated the safety of corticosteroid removal in select patients over 8 to 9 weeks [61]. Many transplant-related medications can have an adverse effect of myelosuppression leading to anemia and thrombocytopenia. These include induction therapies (both antibody depleting and non-depleting antibodies), anti-proliferative agents, and rarely, PSIs [62–64]. Additionally, infectious prophylactic agents such as trimethoprim sulfamethoxazole and valganciclovir can lead to thrombocytopenia [65, 66]. Thus, if a new cell count abnormality is observed, consideration of adjustment to immunosuppression or infectious prophylaxis should be considered.

Palpitations

In heart transplant patients presenting with symptoms of palpitations, an electrocardiogram (ECG) should be performed. Tachyarrhythmias can be divided into supraventricular (SVT) and ventricular arrhythmias. SVT due to atrial fibrillation in patients with a heart transplant should prompt a search for either allograft rejection or the presence of CAV [67]. Atrial flutter should be considered for catheter ablation, as outcomes in transplant patients are similar to non-transplant patients [68]. Adenosine, which acts on the AV node, can be used safely with caution at low doses (typically 3 mg) in patients experiencing a SVT [69]. Calcium channel blockers (CCB) can be utilized but it should be noted that some dihydropyridine CCBs can increase CNI concentrations. Thus, careful monitoring should be pursued. The development of ventricular tachycardia after a heart transplant is associated with long-term outcomes [70] and evaluation for possible ablation therapy should be considered.

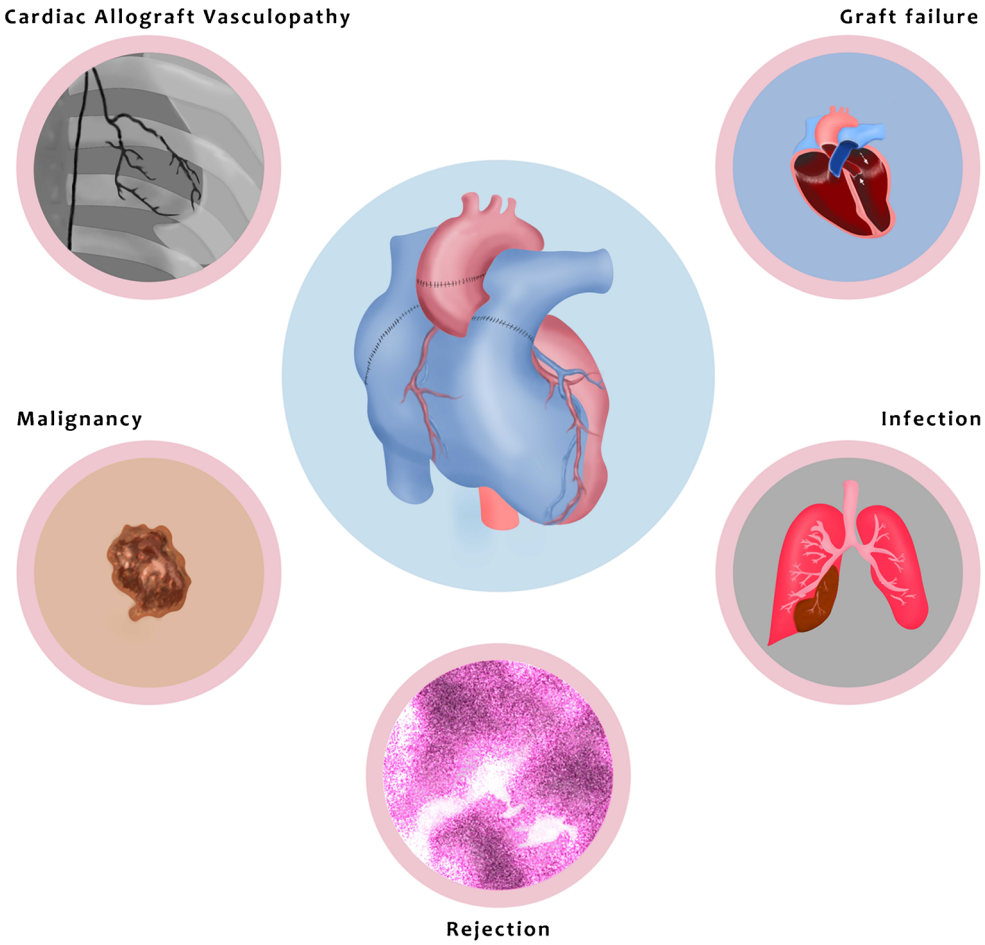

Fig. 1 Summary of complications after heart transplant

Fever

Fever in a patient receiving immunosuppressive therapies after heart transplant should be evaluated with exhaustively. Beyond the post-operative period, fever typically represents infection or inflammation although cases of acute CAV have presented with fever and malaise [71]. The timing after transplant is critical as within 30 days typically results from nosocomial infections while afterwards opportunistic and community-acquired infections occur more commonly [39, 72]. History should include donor and recipient history of infection, immunosuppressive regimen, prior rejection history, exposures, and ATP values via T cell ImmuKnow assay (if available). Evaluation should include skin (with particular attention to sternal wound), examination, infectious lab values, and a low threshold to pursue imaging. Conversely, the use of immunosuppressive medications can mask fevers in the setting of an opportunistic infection. Thus, overall, a high index of suspicion and a low threshold for diagnostic testing and treatment of possible infection should be considered given the risk-benefit ratio in heart transplant patients.

Limitations

This is a review paper of contemporary literature covering commonly seen complications after heart transplantation in adults. The limitations include the lack of high level of evidence randomized controlled trials and large cohort studies.

Future Directions

As heart transplant patients live longer, surveillance for graft rejection will rely upon multi-modality tools including gene expression profiling, cell-free DNA detection, and intragraft microRNA evaluation. Furthermore, the use of immunosuppression will be tailored on a personalized basis utilizing tools including the T cell immune function assay. Overall, a more personalized approach to the care of the heart transplant patient will be seen.

Conclusions

The median survival after transplant is currently 11 years for patients who survive the first year [5]. Complications after

heart transplantation are broad, ranging from mechanical to immunologic-mediated to infectious, and resulting from sequelae of immunosuppressive therapies used to preserve graft function. Additionally, the approach to common medical complaints including shortness of breath, bleeding, palpitations, and fever should be adjusted to the potential diagnoses in heart transplant patients. A thorough understanding of the varying physiology with the transplanted heart is important in the short- and long-term management of these patients.

Compliance with Ethics Guidelines

Conflict of Interest Kevin S. Shah declares no conflict of interest. Jon A. Kobashigawa declares that he has received research grants from Novartis, Alexion, Sanofi, and CareDx.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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