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UPDATES IN ADVANCED HEART FAILURE (E. RAME AND M. ST. JOHN SUTTON, SECTION EDITORS)

Updates on Heart Transplantation

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Abstract
Purpose of Review The purpose of this review is to provide a comprehensive update on recent advances in heart transplantation.
Recent Findings Heart transplantation is now an established therapy for end-stage heart failure, though challenges still exist. However, multiple advances over the past few years will improve the survival and quality of life of heart transplant recipients. These advances include acceptance of previously considered marginal donor hearts, revisions to the donor heart allocation policy, advances in desensitization regimens, tailoring of immunosuppression regimens, and improvement in the diagnosis of rejection and allograft vasculopathy.
Summary Heart transplantation is evolving to provide better quality of life and survival to higher risk recipients with methods to broaden the donor pool, make the best use of existing organs, and refine the management of sensitization and diagnosis of rejection and allograft vasculopathy.

Keywords Heart transplant · Allocation · Mechanical circulatory support · Allograft rejection · Surveillance · Endomyocardial biopsy

Introduction

Dr. Christiaan Barnard performed the world's first human heart transplant over 50 years ago [1] and in the decades, hence, organ transplantation has made marked progress in reducing the morbidity and mortality suffered by patients with heart failure (HF). Heart transplantation remains the definitive therapy for end-stage HF. Worldwide, the annual number of heart transplants is increasing, with 5074 heart transplants performed in 2015 [2•] though challenges continue to exist. Donor supply remains the major rate-limiting step in heart transplantation. In addition, potential recipients of heart transplant are older, more often have mechanical circulatory support (MCS) devices, and have greater degrees of antigen-sensitization prior to transplant listing [3]. However, acceptance of previously considered marginal donor hearts, revisions to the donor heart allocation policy, and advances in desensitization regimens, tailoring of immunosuppression, and the diagnosis of rejection and allograft vasculopathy can address these challenges. In this review, we will provide a comprehensive update on recent advances in heart transplantation and offer insight into future areas of growth.

Broadening the Donor Pool

Given the limited number of hearts available for potential recipients, innovative strategies to increase the potential donor pool include the use of patients with transmittable but treatable diseases such as hepatitis C (hepC) and the use of older donors.

Two major advances have ushered in the use of hepC viremic donors for heart transplant candidates. First, hepC-positivity was previously diagnosed by serologic evidence of prior exposure to the virus; however, the utilization of nucleic acid testing (NAT) to measure viral load allows physicians to better determine which potential donors actually have active hepC viremia and are thus at higher risk of transmission of the virus to the recipient [4]. Second, the advent of antiviral therapies for hepC has led to high cure rates such that development of hepC viremia in the transplant recipient can be

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managed and cured with new direct-acting antiviral therapies with sofosbuvir or ledipasvir [5, 6].In kidney transplant recipients, there is no difference in long-term outcomes between hepC antibody-positive recipients who received kidneys from hepC antibody-positive donors [7].

Furthermore, treatment of hepC infection after kidney transplant with direct-acting antiviral agents is well-tolerated and effective [8]. In the published experience of heart transplantation in the U.S., 13 patients received heart transplants from hepC-positive donors between 2016 and 2017. Nine of 13 patients developed hepC viremia after transplant; 8 were cured with treatment with either ledipasvir-sofosbuvir or sofosbuvir-velpatasvir depending on genotype. The ninth patient undergoing hepC treatment died as result from a pulmonary embolism [9]. There are no current Organ Procurement and Transplantation Network (OPTN) policies preventing transplantation of hepC-viremic organs into non-hepC-viremic recipients; thus, transplant centers willing to utilize this strategy must develop protocols to minimize the risk of using hepC viremic donors in non-viremic recipients with surveillance and antiviral treatment strategies and thus broaden the donor pool.

As the population ages in the U.S., there are a greater number of older patients with end-stage HF. The use of older donors has historically been associated with worse long-term outcomes, with an increased risk of death in donors over 40 [2•]. At a consensus conference held in 2017, 62% of attendees reported their transplant center would not use an older donor (> 50 years) with an older recipient (> 60 years) [10] due to concerns about an increased risk of mortality. A recent analysis of registry data demonstrated no survival disadvantage in recipients of older (> 50 years) donor hearts; however, there was a greater incidence of cardiac allograft vasculopathy (CAV) post-transplant. The use of older donors matched with older recipients serves two purposes: carefully selected older recipients can expect improvement in quality of life and survival after heart transplantation and older donor hearts, which might otherwise be discarded, can be put to life-saving use.

Allocation

The United Network for Organ Sharing (UNOS) serves as the Organ Procurement and Transplantation Network (OPTN) to determine equitable allocation of organs in the U.S. This process is seemingly equitable in that the sickest patients who have been waiting the longest will be considered first when a donor heart becomes available. However, changes in the heart transplant landscape have motivated efforts to improve the current system [11, 12]. There is an increase in candidates awaiting transplantation without a corresponding increase in donors; the highest acuity (Status 1A, 2006 UNOS allocation policy) patients have undesirably high mortality, and advances in durable mechanical support have reduced mortality in this subset of the waiting list. The goals of the revision are to increase transplantation rates for adult candidates with the highest waiting list mortality rates and to achieve the greatest survival benefit for heart transplant recipients.

There are two major problems with the 2006 criteria. First, the system offers inadequate resolution. For example, Status 1A includes patients supported with extracorporeal membrane oxygenation (ECMO), mechanical ventilation, and inotropic support and continuous hemodynamic monitoring, and all have equal urgency. However, heart transplant candidates on ECMO support are more tenuous with lower projected survival than candidates receiving low-dose support from two inotropic agents and continuous hemodynamic monitoring; yet two such patients would receive the same priority under the 2006 3-tiered system. Second, the 2006 system ignores candidates with poor prognosis who would not qualify for traditional Status 1A listing with inotropic support and continuous hemodynamic monitoring, such as those with complex congenital heart disease, restrictive or infiltrative cardiomyopathies, or refractory ventricular tachycardia.

As these disparities were recognized, the UNOS Thoracic Committee determined that the primary areas of allocation that need to be addressed include the limitation of the 2006 tiered system, status of ventricular assist device (VAD) supported patients awaiting transplantation, and improved geographic sharing.

Therefore, as of October 2018, the allocation waitlist system changed to a system of six tiers (from three) with a greater recognition of the use of MCS [13•]. Table 1 illustrates the updated allocation system, in which the 2006 status 1A is divided into three statuses (1–3, by decreasing acuity), status 1B into status 4, and status 2 into 5 and 6. This multi-tiered system prioritizes patients supported with ECMO, non-dischargeable VADs, and mechanical circulatory support (MCS) with life-threatening arrhythmias in the highest tier above those patients with uncomplicated MCS or continuous inotropic support with continuous hemodynamic monitoring. The proposed system also addresses potentially underserved populations, such as adults with congenital heart disease, re-transplantation, restrictive cardiomyopathy, and hypertrophic cardiomyopathy in a separate tier above other outpatients.

Furthermore, when a donor heart becomes available, it will first be available to recipients listed in status 1 and 2 across a 500-mile radius, providing broader sharing to the patients who may have the greatest urgency for heart transplantation. If a heart is not taken by a transplant center, then it returns to the status 3 recipients within the original donation service area.

These revisions should allow for more equitable distribution of the scarce resource of donor organs such that the most critically ill patients are most likely to receive transplantation before the window of viability closes. However, it remains to be seen whether a system that prioritizes ECMO, an unstable

Table 1 Revised Organ Procurement and Transplantation Network (OPTN) heart allocation policy

Status 1	Veno-arterial extracorporeal membrane oxygenation (VA-ECMO)
	Non-dischargeable, surgically implanted, non-endovascular biventricular support device
	MCSD with life threatening ventricular arrhythmia
Status 2	Non-dischargeable, surgically implanted, non-endovascular left ventricular support device (LVAD)
	Total artificial heart, BiVAD, RVAD, or VAD for single ventricle patients
	Mechanical circulatory support device (MCSD) with malfunction
	Percutaneous endovascular MCSD
	Intra-aortic balloon pump (IABP)
	Ventricular tachycardia (VT) or ventricular fibrillation (VF)
Status 3	Dischargeable LVAD for discretionary 30 days
	Multiple inotropes or a single high dose inotrope and hemodynamic monitoring
	MCSD with hemolysis
	MCSD with pump thrombosis
	MCSD with right heart failure
	MCSD with device infection
	MCSD with mucosal bleeding
	MCSD with aortic insufficiency
	VA ECMO after 7 days
	Non-dischargeable, surgically implanted, non-endovascular LVAD after 14 days
	Percutaneous endovascular circulatory support device after 14 days
	IABP after 14 days
Status 4	Dischargeable LVAD without discretionary 30 days
	Inotropes without hemodynamic monitoring
	Congenital heart disease
	Ischemic heart disease with intractable angina
	Amyloidosis, or hypertrophic or restrictive cardiomyopathy
	Heart re-transplant
Status 5	On the waitlist for at least one other organ at the same hospital
Status 6	Adult candidate suitable for transplant

situation for heart transplant candidates, results in more transplantation of unstable patients on ECMO and worse outcomes.

Sensitization

Sensitization is the presence of anti-HLA antibodies in the serum of heart transplant candidates and is a result of prior transplant, blood transfusions, pregnancies, or MCS. Solid phase assays allow for the detection, determination of binding intensity of anti-HLA antibodies, and ability for these antibodies to bind complement. This information can identify patients at greater risk of poor outcomes after transplantation [14]. The most important recent advance in HLA antibody technology is the ability to determine which antibodies can fix complement. As part of the classical pathway of complement activation, the C1-complex is triggered when C1q binds multiple IgG molecules complexed with antigen; this leads to cascade signaling terminating with complement-dependent cytotoxicity (CDC). Thus, the ability of anti-HLA antibodies to bind C1q is a marker of potential in vivo cytotoxicity and C1q binding is associated with poor outcomes in kidney transplant recipients [15, 16].

Sensitized heart transplant candidates often require desensitization therapy to reduce the presence or strength of HLA antibodies prior to transplantation. The goal of desensitization is to expand the donor pool, minimize time on the wait list, and reduce the risk of antibody-mediated rejection. Treatment options include intravenous immunoglobulin (IVIG) and plasmapheresis to neutralize and remove circulating antibodies, respectively [17]. Furthermore, medications including rituximab (a chimeric monoclonal antibody against CD20 expressed on B cells) and bortezomib (a selective 26S proteasome inhibitor that depletes plasma cells) can be incorporated in a desensitization plan [18]. Lastly, the agent eculizumab (a humanized anti-C5 monoclonal antibody), which inhibits C5 cleavage to C5a and C5b to prevent formation of the C5b-9 membrane attack complex, has been studied as a potential agent to prevent injury from antibodies and possibly to reduce circulating antibodies in highly sensitized patients [19]. Results from the on-going De-novo Use of Eculizumab

Alongside Conventional Therapy in Pre-sensitized Patients Receiving Cardiac Transplantation (DUET) trial will demonstrate the safety and efficacy of eculizumab to prevent AMR. We anticipate therapies to reduce antibodies in highly sensitized patient will evolve.

Immunosuppression

The mainstay for immunosuppression after heart transplantation is the use of calcineurin inhibitors (CNIs), which have significantly increased the life expectancy of patients after transplantation. However, given the nephrotoxic effects of CNIs, research has focused on CNI-free regimens with early conversion to proliferation signal inhibitors (PSIs; sirolimus and everolimus) in order to avoid long-term exposure to CNIs. PSIs function by inhibiting the proliferation of T cells, B cells, and vascular smooth muscle cells in response to growth factor and cytokine signals. Both sirolimus and everolimus reduce the incidence of acute rejection and prevent development of cardiac allograft vasculopathy (CAV) in randomized trials [20, 21]. In a retrospective cohort, conversion from a CNI to PSI in 402 HT recipients resulted in a reduction in long-term mortality, with attenuated cardiac allograft vasculopathy (CAV) progression, and a decrease in CAV-related events. In a randomized trial of 115 de novo heart transplant recipients, the use of everolimus, cyclosporine, mycophenolate (MMF), and corticosteroids (with withdrawal of cyclosporine after 7 weeks) was compared with conventional treatment with cyclosporine, MMF, and corticosteroids [22]. Patients who received early everolimus with cyclosporine withdrawal had improved renal function and a lower incidence of CAV 1 year after transplantation, at the cost of a higher incidence of biopsy-proven rejection. Thus, early utilization of PSI with elimination of CNI may preserve renal function and reduce CAV incidence after heart transplantation, but the CNI to PSI conversion is not without risks of intolerance and rejection.

There are high rates of intolerance associated with PSIs, specifically related to cytopenias, mouth ulcers, gastrointestinal upset, dependent edema, and impaired wound healing. There is also a real risk of rejection with CNI withdrawal and thus this strategy is reserved for patients who are at low risk of rejection. Nonetheless, for those who can tolerate PSIs, their use in place of CNI early post-transplant may prolong graft survival and maintain long-term renal function.

Steroids are started at time of transplant and typically weaned off by the first-year post-transplant. Steroid-free regimens have gained favor as there is less benefit seen in the use of steroids 1-year after heart transplant [23]. Small studies have shown that a steroid-free maintenance immunotherapy is feasible and shows similar survival and episodes of rejection post-transplant [24]. In a randomized trial of tacrolimus monotherapy compared with tacrolimus and mycophenolate mofetil [25], corticosteroids were discontinued in both arms at 8 to 9 weeks post-heart transplant. There was no difference in long-term survival, CAV incidence, or rejection. Thus, it may be feasible in selected patients after transplant to wean corticosteroids and MMF early after cardiac transplantation with long-term safety.

Rejection

Allograft rejection remains an important cause of morbidity and mortality post-transplant, with the risk at its greatest in the first 6 months. Rejection of the transplanted heart can be driven by a cellular (ACR) or an antibody-mediated (AMR) process.

While endomyocardial biopsies (EMB) are the gold standard for diagnosis of rejection, techniques for predicting and detecting graft rejection have progressed beyond simple histopathology and immunopathology. The EMB procedure has limitations including sampling error, invasiveness, and poor inter-pathologist concordance [26, 27]. Three major advances in the diagnosis of rejection include gene expression profiling, cell-free DNA detection, and microarray technology (Fig. 1).

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 and the gene expression profile (GEP) test (AlloMap®, CareDx Inc., San Francisco, CA), an 11-gene expression signature, derived from peripheral blood mononuclear cells, has emerged as a non-invasive test with a high negative predictive value for the presence of ACR [28]. In a randomized trial, GEP was shown non-inferior to the biopsy in the diagnosis of ACR [29••] and also useful in early post-transplant [30]. One role of the GEP is to screen low-risk patients at pre-determined intervals with biopsies performed only if the GEP score is abnormal. However, it must be emphasized that patients with a history of, or risk factors for, AMR are not candidates for GEP screening, as the test has only been validated for ACR.

Serum biomarkers represent another attractive strategy for the detection of rejection. After organ transplantation, donor-derived cell-free DNA (ddcfDNA) is detectable in the recipient's blood and urine [31]. However, a small fraction of this ddcfDNA is from the graft; the development of digital droplet PCR and parallel sequencing allowed for the opportunity to monitor ddcfDNA kinetics after transplantation [32].In stable heart transplant recipients, there is a steady decline in ddcfDNA from first day post-transplant to 1 week after transplant [33]. In cases of rejection, there is a rise of ddcfDNA and a prospective cohort study demonstrated diagnostic accuracy with an area under the receiver operating characteristic curve of 0.83 [33]. The use of this biomarker may serve as an

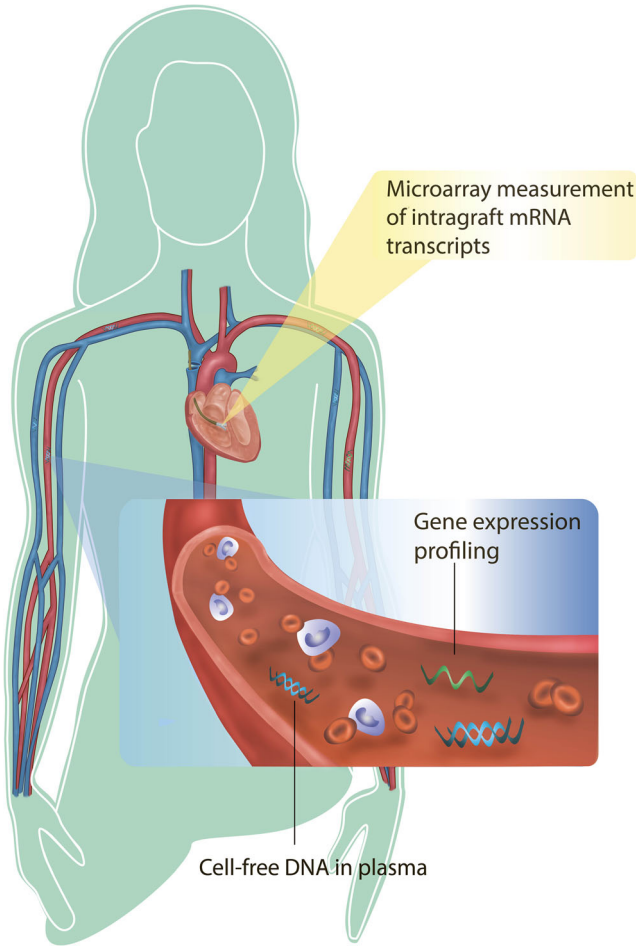

Fig. 1 Non-invasive strategies for graft rejection surveillance: mRNA transcripts from endomyocardial biopsies, gene expression profiling, and measurement of donor-derived cell-free DNA are tools to further understand and characterize allograft rejection

additional tool for monitoring of allograft health to minimize the need for EMB post-transplantation.

Evaluation of EMB tissue at a molecular level represents another novel approach to further understand allograft rejection and possibly guide treatment. The Molecular Microscope MMDx® system uses microarrays to measure mRNA levels followed by automated analysis routines for interpreting the results [34]. EMB samples from patients who have undergone heart transplantation are being studied to improve the understanding of relevant biological pathways potentially amenable to treatment [35]. The output from this assay includes a probability of T cell or antibody-mediated rejection, as well as quantification of acute parenchymal and irreversible injury. Rejection-associated transcripts can be used to estimate the probability of rejection based on mRNA expression, potentially improving our diagnostic accuracy beyond histology interpretation [36]. Table 2 provides a summary of novel strategies for rejection surveillance.

Cardiac Allograft Vasculopathy

CAV is a form of chronic rejection of the transplanted heart. CAV is characterized by pan-arterial disease with concentric longitudinal intimal hyperplasia and diffuse narrowing of the coronary vessels [20, 37]. The development of CAV is thought to be an inflammatory process and the incidence affects up to 50% of recipients within 10 years of transplantation [38]. The diagnosis is made via coronary angiography, but the use of intravascular ultrasound (IVUS) can detect the intimal thickening and increase sensitivity for CAV detection. An increase in maximal intimal thickness greater than 0.5 mm during the first post-transplant year is associated with a poor prognosis [39].

Non-invasive approaches to detect CAV offer advantages by reducing the risk associated with coronary angiography and IVUS. Computed tomography angiography (CCTA) is an attractive option as it provides non-invasive anatomical information including stenosis severity and plaque composition. A meta-analysis of 615 patients comparing CCTA with angiography demonstrated mean weighted sensitivity of 94% and specificity of 92% for significant CAV. When compared with IVUS, the mean weighted sensitivity and specificity were 81% and 75% to detect CAV [40]. The use of CCTA for CAV surveillance will likely supplant invasive angiography as larger studies demonstrate its utility.

Table 2 Pros and cons of novel post-transplant surveillance tests

	Description	Pros	Cons
Gene expression profiling (AlloMap®)	Utilizes measurements of gene expression involved in rejection	• High negative predictive value • Non-invasive	• Limited to ACR • Not valid if used within 2 months after transplant
Donor-derived cell-free DNA	Detectable levels rise from graft injury related to rejection	• Non-invasive • May provide pre-clinical signal of rejection	• Not studied in large cohorts • May not differentiate mechanism of rejection
Molecular Microscope MMDx® system	Uses microarrays to measure mRNA levels	• Provides insight into ACR/AMR	• Requires EMB sample • Clinical management trials to be determined

Conclusion

The field of heart transplantation is evolving with a greater emphasis on equity and providing a scarce resource to patients in greatest need. Areas of growth include expanding the donor pool with the use of hepC donors and older donors; more equitable distribution of donors through a new allocation policy, advances in desensitization strategies, and improvements in our ability to diagnose rejection and allograft vasculopathy. We anticipate a more personalized approach to post-transplant care, incorporating individualized immunosuppression regimens, biomarkers, and advanced imaging to predict risk and optimize therapy. Our understanding of personalized and precision care in transplant cardiology will likely be the next key area of growth as we continue to refine our ability to improve the survival and quality of life of heart transplant recipients.

Compliance with Ethical Standards

Conflict of Interest Kevin S. Shah and Michelle M. Kittleson declare no conflicts of interest. Jon A. Kobashigawa reports grants from Novartis, grants from Alexion, grants and personal fees from CareDx, grants from Sanofi, all outside the submitted work.

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 importance
- •• Of major importance

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