STATE-OF-THE-ART PAPER

The Changing Face of Heart Transplantation

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It has been 40 years since the first human-to-human heart transplant performed in South Africa by Christiaan Barnard in December 1967. This achievement did not come as a surprise to the medical community but was the result of many years of early pioneering experimental work by Alexis Carrel, Frank Mann, Norman Shumway, and Richard Lower. Since then, refinement of donor and recipient selection methods, better donor heart management, and advances in immunosuppression have significantly improved survival. In this article, we hope to give a perspective on the changing face of heart transplantation. Topics that will be covered in this review include the changing patient population as well as recent advances in transplantation immunology, organ preservation, allograft vasculopathy, and immune tolerance. (J Am Coll Cardiol 2008;52:587–98) © 2008 by the American College of Cardiology Foundation

It has been 40 years since the first human-to-human heart transplant performed in South Africa by Christiaan Barnard in December 1967 (1). This achievement did not come as a surprise to the medical community but was the result of many years of early pioneering experimental work by Alexis Carrel, Frank Mann, Norman Shumway, and Richard Lower (2–4). Media attention surrounding the first heart transplants was enormous as each patient's daily progress was followed very closely and reported worldwide (1). The first heart transplant patient, Mr. Washkansky, had a good early recovery but unfortunately died of pneumonia 18 days later. The second heart transplant patient, Mr. Blaiberg, was the first patient to leave the hospital and returned to a relatively normal life. It was Mr. Blaiberg's success perhaps more than any other factor that led to guarded optimism that heart transplantation would eventually prove to be a valuable treatment option (2).

This initial enthusiasm was, however, quickly curbed when it became evident that survival was usually measured in terms of days or weeks (1). Inadequate understanding of early post-operative complications as well as a lack of tools to address the problems of acute rejection and opportunistic infection led to initially poor results. Allograft vasculopathy as a cause of graft failure and death was also recognized when Mr. Blaiberg sadly died of a myocardial infarction 19 months after his heart transplantation. This came as a surprise to the medical profession, which had not anticipated that coronary artery disease in a transplanted heart could progress so rapidly (2).

Over the next 2 decades, refinement of donor and recipient selection methods, better donor heart management, and the introduction of cyclosporine as the main immunosuppressive agent significantly improved survival. With a 1-year survival approaching 90%, a 5-year survival rate of approximately 70%, and a median survival in excess of 10 years, heart transplantation is now a valuable option for selected patients with end-stage heart failure (Fig. 1) (5). The field of heart transplantation is constantly evolving. Advances in organ preservation, immune monitoring, and immunosuppressive regimens are likely to lead to further improvement in the quality and the length of life of heart transplant recipients (Fig. 1). In this article, our objective is to give a perspective on the changing face of heart transplantation. Topics that will be covered include the changing patient population as well as recent advances in transplantation immunology, organ preservation, allograft vasculopathy, and immune tolerance.

The Changing Patient Population

The face of heart transplantation is slowly changing. At the same time as older patients are being considered for heart transplantation, a greater proportion of younger patients being referred for evaluation have complex congenital heart disease (CHD) (3,5). There is also a slow increase in both the number of patients who require mechanical circulatory support (MCS) as a bridge to transplantation and the number of retransplant candidates (5). This changing patient population brings new challenges to the transplant physicians. Among them, the risk of having preformed antibodies directed against the donor heart (sensitized patients) is particularly challenging as it may increase the risk of rejection and allograft vasculopathy (5–7). Patients with CHD often have a more complex anatomy and are also

at an increased risk of periopera-
tive bleeding and mortality (8).

Once considered an absolute
contraindication to transplanta-
tion, older recipient age is now
seen as a relative contraindication
(9). Older recipient age is usually
considered a risk factor for re-
duced post-transplant survival,
although many single-center
studies report excellent survival
in carefully selected older recipi-
ents (9,10). The incidence of re-
jection is usually lower in older
recipients while the incidence of
infection and allograft vasculopa-
thy appears to be higher (5,9).

With the advances made in
cardiac surgery, an increasing
number of patients with CHD are now surviving into
adulthood. Many patients with CHD develop heart failure
later in life, despite repair or palliation or as a result of
uncorrected lesions (8,11). The most common congenital
lesions in patients referred for transplantation include trans-
position of great arteries with a failing right ventricle, failed
Fontan procedures, palliated single ventricle, Ebstein's
anomaly, and tetralogy of Fallot with severe right ventricular
dysfunction (8,11). According to the International Society
for Heart and Lung Transplantation (ISHLT) database,

CHD is identified as one of the strongest risk factors for
1-year mortality after heart transplantation in adults (5,8).
In contrast, in those who survive 3 years, CHD disease has a
10-year survival advantage independent of age. Factors that
may contribute to this earlier mortality include: 1) adhesions
from prior surgeries; 2) a higher incidence of collateral vessels,
which increases the risk of bleeding; 3) technically more
challenging surgery because of the unusual anatomy; and
4) a higher incidence of sensitized patients. The risk of
early mortality may also be different according to the
underlying pathology, with more favorable outcomes for
simple uncorrected lesions than for complex uncorrected
lesions.

In the last decade, there has also been an increase in the
number of patients requiring MCS as a bridge to transplan-
tation (12). This technology has allowed many severely ill
adult and pediatric patients to survive until a suitable donor
heart became available. Patients who require MCS are at
increased risk for rejection, infection, stroke, and bleeding.
The need for transfusions and possibly the mechanical
devices themselves increase the risk of pre-sensitization
(5–7). Based on the ISHLT database, survival at 1 and 5
years is decreased in patients requiring MCS but still higher
than 80% and 70%, respectively (5).

With the increasing number of patients transplanted at
early ages, it is also expected that the need for retransplan-
tation will become more common in the future. For now,
however, retransplantation comprises only a small minority
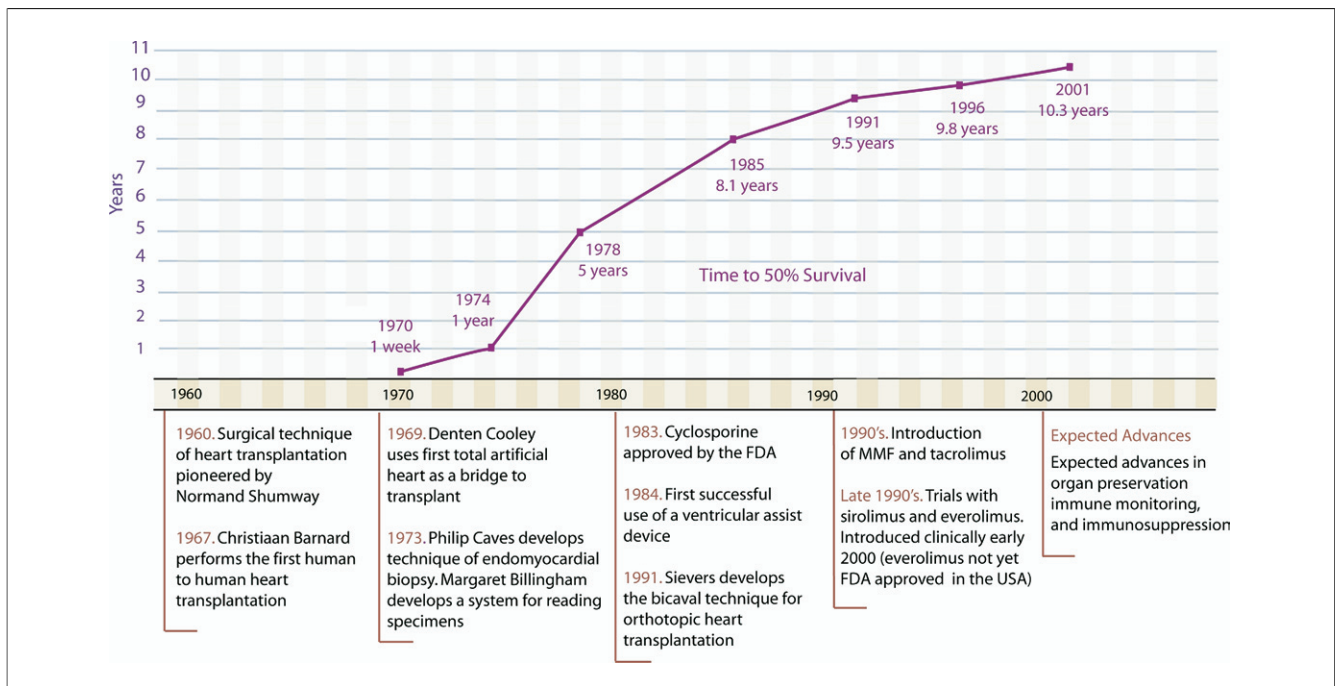(≈3%) of heart transplants (5). Overall survival rates for

Figure 1   Historical Perspective of Heart Transplantation

The figure describes the major landmarks of heart transplantation associated with progressive improvement
in survival. FDA = Food and Drug Administration; MMF = mycophenolate mofetil. Adapted, with permission, from Hunt (1).

retransplant patients are significantly lower than for other transplant patients, possibly reflecting an increased risk of allosensitization as well as the consequence of years of immunosuppression (5,13,14). Risk factors for poor outcome include retransplantation early after primary transplantation (<6 months), retransplantation for acute rejection, or early allograft failure and retransplantation in an earlier era (13,14). When selection criteria for retransplantation excluded retransplantation for primary allograft failure and intractable acute rejection occurring less than 6 months after transplantation, 1-, 2-, and 4-year survival rates after retransplantation were comparable to those after primary transplantation (13,14).

Advances in Donor Allocation and Selection

In the U.S., the organization United Network for Organ Sharing is contracted by the federal government to regulate donor heart allocation and has a priority system that is based on the severity of cardiac illness, geographic distance between donor and recipient, length of time on the waiting list, and ABO blood group compatibility (11). At the current time, the physiological limit of approximately 4 to 5 h of ischemic time precludes a national sharing of donor hearts or matching donor hearts according to human leukocyte antigen (HLA) compatibility (10). The algorithm for allocation of donor hearts used by the United Network for Organ Sharing was changed in January 1999 to better account for medical urgency and to decrease waiting times for blood type O recipients (15). Medical urgency is 2-tiered in the 1989 system and 3-tiered in the new system; the new allocation algorithm also allows an individual with life-threatening ventricular arrhythmias to be listed in the highest urgency status (15). In recent years, the widening gap between the number of waiting recipients and the number of donors has resulted in a continuing trend toward transplanting urgent status recipients and to a liberalization of donor acceptance criteria (16). Despite these changes, post-transplant survival has remained constant mainly due to advances in treatment (16).

Donor heart acceptance is a 2-phase process. The first step is to rule out any contraindication to heart donation such as significant heart dysfunction, CHD, transmissible diseases, or malignancies (except primary tumors of the central nervous system with low metastastic potential). The second step is to match a specific donor to a suitable transplant candidate. In heart transplantation, matching is based on ABO blood group compatibility (not identity) and compatibility of body size. Although adult donor hearts must be ABO compatible with the recipient, this concept has been recently challenged in infants (age <12 months) by the successful performance of ABO incompatible heart transplants (11,17). In their landmark study, West et al. (17) have shown that in infants serum titers as well as production of anti-A and anti-B antibodies are usually low enough to allow transplantation with ABO incompatible

donor hearts. Matching donor and recipient for size is especially important in patients with pulmonary hypertension. In general, a height and weight difference of up to 20 percent is tolerated; in potential recipients with significant pulmonary hypertension, donor size equal or higher than the recipient is usually recommended. In pediatric patients, in order to address donor shortage, a more liberal strategy utilizing an oversized donor has been advocated by many centers with successful results (11).

Donor characteristics that have been associated with outcome include age, left ventricular hypertrophy, and gender mismatches. The use of older donor hearts (>40 year old) is associated with higher perioperative mortality and a higher incidence of later cardiac allograft vasculopathy (5). Donor left ventricular hypertrophy, defined by a left ventricular wall thickness greater than 14 mm has also been associated with decreased long-term survival in some studies (18). Recent studies have also called attention to gender mismatch in cardiothoracic transplantation. According to the ISHLT database, female donor gender is associated with worse 5- and 10-year survival in male recipients (5). Donor heart allocation from hepatic C positive patients is also sometimes considered for recipients on an alternate list. A recent study from the U.S. Scientific Registry of Transplant Recipients has demonstrated that donor hepatitis C virus status is associated with a decrease in 1- and 5-year mortality in recipients older than 39 years irrespective of recipient hepatitis C virus status (19).

According to the ISHLT registry, high center volume is associated with better post-transplant outcomes (5). In an effort to improve survival, the federal regulatory agencies determined that a heart transplant program must do at least 12 transplants per year to receive federal reimbursement, according to the Centers for Medicare and Medicaid Services.

Advances in Surgical Technique and Organ Preservation

The surgical techniques for heart transplantation include 2 basically different surgical approaches (i.e., orthotopic [the donor heart implanted in the normal place of the native heart] and heterotopic [donor heart implanted beside the native heart]) (20,21).

The biatrial technique for orthotopic heart transplantation was first introduced in a dog model by Lower and Shumway in 1960 (22). Preservation was provided by the use of topical hypothermia induced by immersion of the graft in iced saline (3,22). In 1991, Sievers et al. (23) described a variation of the orthotopic procedure termed the bicaval technique where the donor right atrium is attached directly to the inferior and superior vena cava and the left atrial anastomosis is done as a cuff. Compared with the classical biatrial approach, the bicaval approach results in less disruption of the atrial geometry, better right ventricular function, less tricuspid and mitral regurgitation, and less

sinus node dysfunction (24). Despite increasing use of the bicaval technique, tricuspid regurgitation remains a problem early and late after heart transplantation. Adding a tricuspid annuloplasty to the transplant operation has been recently shown to decrease the incidence of tricuspid regurgitation and may even improve survival (25).

Heterotopic heart transplantation was first performed by Barnard in 1974 as a left ventricular bypass and involves placing a donor heart in the right lower thorax where it is anastomosed to work in parallel to the recipient heart, which is left intact (2). The concept of having the donor and native heart side by side was more appealing in the early era of heart transplantation when the incidence of early graft failure was high. Although rarely done today, there remain 2 possible indications for heterotopic heart transplantation: 1) patients with elevated pulmonary hypertension in whom the donor right ventricle would be unable to tolerate the increased afterload; and 2) significant size mismatch (donor/recipient weight ratio <75%), especially seen in pediatric patients. Heart-lung transplantation may also represent an option for patients with irreversible elevation in pulmonary hypertension.

Recent advances in organ preservation may also lead to further improvement in outcomes. One of the most promising new technologies is normothermic organ preservation, which provides warm blood perfusion of the donor organ, potentially decreasing reperfusion injury and graft dysfunction. If proven effective, this technology may decrease early graft failure and allow increased utilization of available organs. Its potential to decrease ischemic time may also give greater opportunity for prospective cross-matching in heart transplantation (26).

Advances in Immunology

Immunologic barriers remain the central issue in transplantation medicine. An evolving understanding of the pathways involved in immune activation has led to many breakthroughs in transplantation medicine, including the development of many novel immunosuppressive agents. In this section, we will review the pathways involved in the alloimmune response, the principles of immune monitoring, as well as recent advances in immunosuppressive therapies.
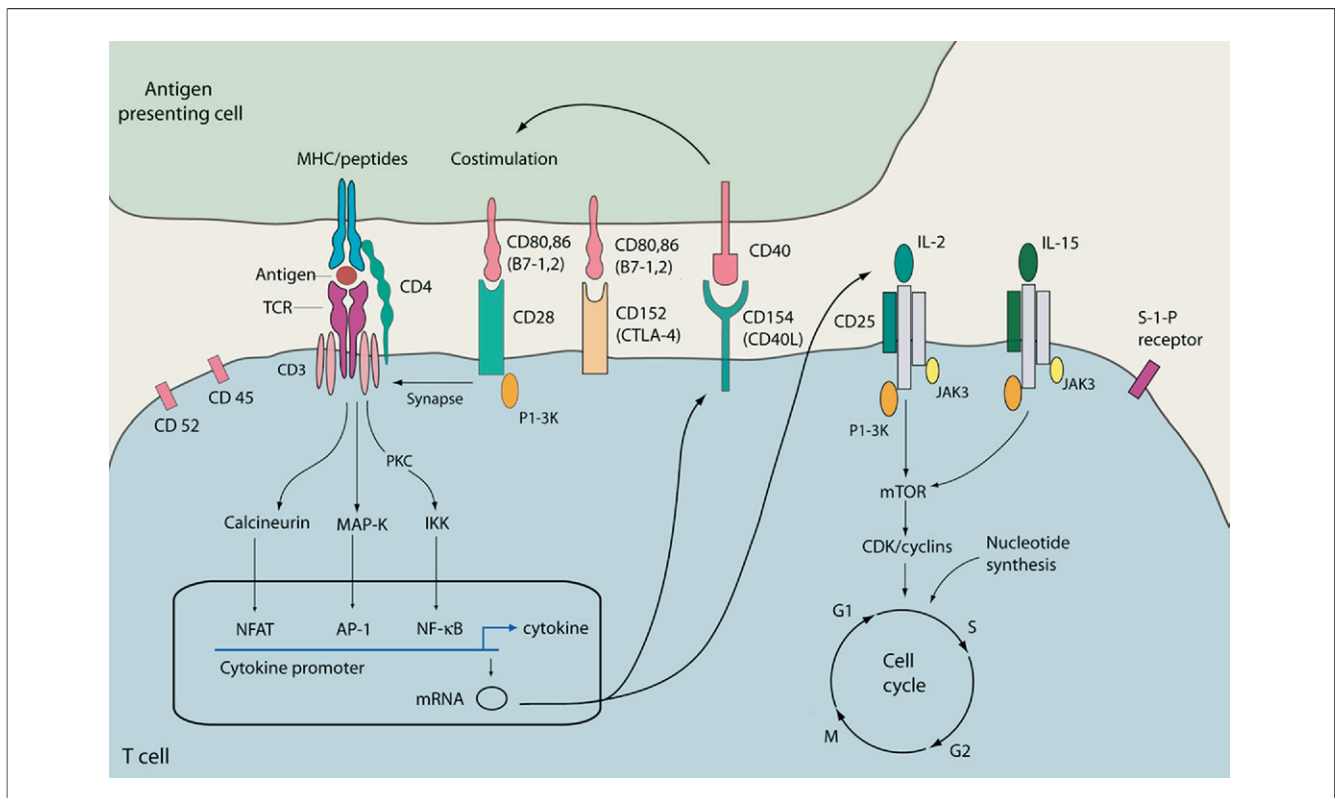

Figure 2   Steps in T Cell Activation

The alloimmune response often requires activation of multiple signaling pathways. The first signal is provided when antigen-presenting cells and antigens activate the T cell receptor. Costimulation (signal 2) occurs when CD80 (B7-1) and CD86 (B7-2) on the antigen-presenting cells engage CD28. Both signals activate important signal transduction pathways (calcineurin, RAS-mitogen-activated protein kinase [MAP-K] pathway, and the nuclear factor-kappa B [NF-kB] pathway). These pathways lead to the expression of many molecules, including interleukin (IL)-2 and IL-15. Interleukin-2 and other cytokines then activate the "target of rapamycin" pathway to provide the trigger for cell proliferation (signal 3). AP-1 = activating protein 1; CDK = cyclins-dependent protein kinase; IKK = serine-threonine protein kinase; JAK3 = Janus kinase 3; MHC = myosin heavy chain; mRNA = messenger ribonucleic acid; mTOR = mammalian target of rapamycin; NFAT = nuclear factor of activated T cells; PKC = protein kinase C; S-1-P = sphingosine-1-phosphate; TCR = T cell receptor. Adapted, with permission, from Halloran (28).

The alloimmune response. T cell lymphocyte activation plays a central role in the alloimmune response (Fig. 2). Both naïve and memory lymphocytes may be involved, including memory lymphocytes that may have been previously stimulated by viral antigens that can cross-react with HLA antigens (27,28). The alloimmune response usually starts with the activation of antigen-presenting cells of donor (usually dendritic cells) and host origin. Once activated in the graft and surrounding tissue, these cells migrate to secondary lymphoid organs where they may engage alloantigen reactive naïve T cells and central memory T cells (28,29). Naïve T cells and memory T cells may recirculate in the secondary lymphoid organs or undergo clonal expansion and differentiation into effector cells when activated. Some direct antigen presentation to antigen-experienced cells by donor cells such as graft endothelium may also occur (28,30).

In recent years, it has become clear that T cell activation requires the stimulation of multiple signaling pathways. At least 3 signals seem to be required to cause an effective alloimmune response (Fig. 2) (28). The first signal originates from the interaction between the major histocompatibility complex/peptide complex and the T cell receptor/CD3 complex. Antigen-presenting cells, especially dendritic cells, provide costimulation when the CD80 and CD86 (B7) interact with the CD28 on T cells. Costimulation is also influenced by the interaction of CD80 and CD86 with CD152 (CTLA-4) as well as the interaction of CD40 and CD154 (CD40 ligand). These signals lead to the activation of 3 transduction pathways: the calcium calcineurin pathway, mitogen-activated protein kinase pathway, and the nuclear factor-kappa B pathway (28,31). The activation of these pathways, in turn, leads to the expression of cytokines, namely interlukin-2 as well as many molecules such as CD154 and CD25. The third signal of the alloimmune response occurs when interleukin-2 and other cytokines activate the target of rapamycin pathway that leads to cell proliferation and differentiation and, therefore, a large number of effector cells.

B cells are activated when antigens interact with B cell receptors, usually in secondary lymphoid organs and possibly in the transplant organ. B cell activation is also mediated through the interaction between B and T cells through CD40/CD40L and B71-2/CD28 as well as CTLA-4− and CD20-mediated activation. Complement and inflammatory mediators are also activated and contribute to the alloimmune response (28).

Cardiac rejection. There is growing acceptance that rejection, an immune-mediated allograft injury, may be caused by both cellular- and antibody-mediated processes (32–34). Recent studies suggest that antibody-mediated rejection (AMR), also known as humoral rejection, is associated with more severe hemodynamic compromise at presentation and a greater risk of allograft vasculopathy and mortality (33,34).

In cellular rejection, effector T cells mediate an inflammatory response that leads to infiltration of the myocardium by activated macrophage, effector T cells, and plasma cells. The characteristic lesion of cellular rejection represents mononuclear cells invading the myocardium. Cellular rejection is classified into 3 classes depending on the extent of cellular infiltration and myocyte damage. In the internationally accepted grading system for cellular rejection, grade 2R (previously 3A) or higher is considered clinically significant cellular rejection (35,36).

Antibody-mediated rejection occurs when alloantibody against donor antigens targets capillary endothelium (32–34). Although the significance of AMR is increasingly recognized, no firm consensus has yet been reached on its recognition and diagnosis either histopathologically or immunologically (36). Antibody-mediated rejection is usually diagnosed histologically by demonstration of capillary injury with endothelial cell swelling and intravascular macrophage accumulation. Positive immunofluorescence or immunoperoxidase staining for AMR (positive CD68, C4d, or C3d complement fragments) further supports the diagnosis (36). Emerging literature also suggests that positive immunofluorescence for both C4d and C3d complement fragments may be associated with clinical allograft dysfunction (37).

Advances in immunosuppression. The goal of immunosuppression is to prevent or treat rejection while minimizing the risk of infection or cancer. In general, immunosuppression may be achieved by blocking lymphocyte activation or response pathways, depleting lymphocytes, or diverting lymphocytic traffic (28,38). The success of heart transplantation has been closely related to the discovery of effective immunosuppressive regimens. In the early 1980s, the introduction of cyclosporine as the mainstay of immunosuppressive regimens was followed by a significant improvement in survival of heart transplant recipients (Fig. 1). Since then, other agents have been introduced, and several studies have tried to answer important questions concerning immunosuppression (e.g., the need for early induction therapy, the best combination of immunosuppressive agents, the safety of early withdrawal of steroids, and the lowest possible maintenance dose of immunosuppression) (Table 1).

Induction therapy refers to the use of more intense immunosuppression in the initial days after transplantation. The rationale of induction therapy is to provide more intensive immunosuppression at the time when the alloimmune response is most intense. It may also be used to permit delayed initiation of calcineurin inhibitors (CNIs) for maintenance immunosuppression in patients with significant renal failure (RF). Agents used for induction may be divided into 2 categories: 1) depleting antibodies (e.g., polyclonal antibodies [horse or rabbit antithymocyte globulin], anti-CD3 antibodies [OKT3], human monoclonal anti-CD52 [alentuzumab]); or 2) nondepleting antibodies or fusion proteins (e.g., anti-CD25 antibodies [daclizumab, basiliximab] or fusion proteins with natural binding properties currently being studied, e.g., CTLA4-Ig [LEA29Y]) (39). Although induction therapy is used by approximately one-half of transplant programs, a

Table 1	Immunosuppressive Agents in Heart Transplantation	
Immunosuppressive Agent	**Target Class**	**Comment**
Glucorticosteroid	Multiple targets including inhibition of APC and nuclear transcription	Usually weaned during the first year
Calcineurin inhibitors		
Cyclosporine	Cyclophilin	Cyclosporine favored in patients with poorly controlled diabetes mellitus; tacrolimus may be associated with decreased rejection episodes
Tacrolimus	FKBP12	
Mycophenolate mofetil	Purine synthesis inhibitors	Has replaced azathioprine in combination regimens
Proliferation signal inhibitors Sirolimus Everolimus (not yet FDA approved)	Target-of-rapamycin	Sirolimus may reduce the progression of allograft vasculopathy and malignancy; associated with poor wound healing
Polyclonal antibody: horse or rabbit antithymocyte globulin	Depleting antibodies against T cells	Selective use in the treatment of severe cellular rejection or in induction therapy
Rituximab	B-cell–depleting monoclonal anti-CD20 antibody	Selective use in the treatment of humoral rejection
Daclizumab, basiliximab	Anti-CD25 antibody	Selective use for induction therapy
Alemtuzumab	Anti-CD52 antibody	Selective use for induction therapy (preliminary experience in heart transplantation), case reports of its use in refractory rejection
Intravenous immunoglobulin	Multiple sites of actions including interference with F_c receptors on the cells of the reticuloendothelial system	Selective use in the treatment of humoral rejection or sensitized patients
CTLA-4-Ig (LEA29Y) (fusion protein)	Costimulation signal inhibitor	In phase III trials in renal transplantation

APC = antigen-presenting cell; FDA = Food and Drug Administration.

survival benefit attendant on its use has not been clearly established (39–41). Also, concerns about the long-term complications have been suggested by studies linking OKT3 use with a greater risk of lymphoproliferative disorders (39,42). At this time, the weight of the evidence may support a selective use of induction agents in highly sensitized patients or patients with severe RF at the time of transplantation.

The goal of maintenance immunosuppression is to achieve host-graft adaptation while minimizing the risk of infection or cancer. Most cardiac transplant programs use a triple therapy for maintenance immunosuppression consisting of corticosteroids (usually prednisone), a CNI (cyclosporine or tacrolimus), and an antiproliferative agent (usually mycophenolate mofetil) (Table 2). Prednisone is used early after heart transplantation and usually tapered to low doses or withdrawn during the first year. There are 2 general approaches to steroid withdrawal: early withdrawal within the first month after transplantation or late withdrawal between 6 to 12 months post-transplant. Late steroid withdrawal may have the advantage of maintaining more intensive therapy in the first 6 months when the risk of rejection is still high (11,43,44). There is particularly strong interest in minimizing steroid use in children, as it may impair normal growth.

The use of tacrolimus in heart transplantation has steadily increased, and it now is the most commonly used CNI (5,45). In comparing CNIs, tacrolimus is associated with a decreased incidence of rejection episodes, although a survival benefit has not been clearly demonstrated (46). Most programs, however, individualize the choice of CNI depending on the risks profile of the patient. Tacrolimus is favored in the presence of a higher risk of rejection,

Table 2	Maintenance Regimens Used in Heart Transplantation	
Regimens*	**Indication or Characteristic**
Calcineurin inhibitor and mycophenolate mofetil	Most common regimen used; older transplant patients may still be on a calcineurin inhibitor and azathioprine combination
Calcineurin inhibitor and proliferation signal inhibitor	Regimen often considered in patients with established allograft vasculopathy or malignancy
Mycophenolate mofetil and proliferation signal inhibitor	Calcineurin-free regimen considered in patients with severe renal insufficiency
Tacrolimus monotherapy	Preliminary data suggest the safety of tacrolimus monotherapy in heart transplantation (45)

*Corticosteroids usually part of all regimens during the first year.

pre-existing hypertension, or hyperlipidemia, while cyclosporine is favored in the presence of diabetes mellitus. The use of mycophenolate mofetil has replaced the use of azathioprine, which was the first immunosuppressive agent to achieve widespread use in heart transplantation (1). More recently, target of rapamycin inhibitors or proliferation signal inhibitors (sirolimus and everolimus) have been shown to decrease the progression of allograft vasculopathy and cancer as well as provide resistance to rejection (47–49). Poor wound healing is, however, a side effect associated with sirolimus and probably to a lesser degree with everolimus (50). In patients with established allograft vasculopathy, sirolimus has been demonstrated to decrease the progression of allograft vasculopathy and occasionally leads to some reversal of the process (48,51). In patients with severe RF, calcineurin-free regimens (combining sirolimus and mycophenolate mofetil) late after transplantation can improve renal function without increasing the risk of rejection (52,53). A recent study also suggests that belatacept, a costimulatory signal inhibitor (previously referred to as LEA29Y), could represent an alternative to CNIs (54). In a phase II multicenter noninferiority trial in de-novo renal transplant recipients, Vincenti et al. (54) showed that there was no significant difference in acute rejection rates between belatacept and cyclosporine. Interestingly, belatacept-treated patients demonstrated significantly lower rates of tubular atrophy and interstitial fibrosis. Phase III clinical trials of belatacept are ongoing in renal transplantation. If proven efficacious and safe, belatacept will most probably undergo study in heart transplantation. Also, individualization of immunosuppression with better immune monitoring and pharmacogenomics will eventually play a greater role in optimization of therapy (55).

Methods for managing acute rejection are also evolving. In general, the management strategy for acute rejection depends on the histological type of rejection (cellular vs. AMR) as well as its severity (hemodynamic compromise and/or high histological grade). A high-dose corticosteroid (3-day course of methylprednisolone 1 g daily) is used for significant cellular rejection (>2R in the new ISHLT classification) or any rejection-associated hemodynamic compromise. Lymphocyte-depleting agents such as antithymocyte globulin are also considered in patients with hemodynamically compromising or high-grade (3R) cellular rejection. As clinical experience is increasing, the treatment of AMR is being better defined (34). Severe hemodynamically compromising AMR is usually treated with high-dose corticosteroids and plasmapheresis followed by intravenous immunoglobulin or rituximab (a B-cell–depleting monoclonal anti-CD20 antibody). T cell depleting antibodies such as antithymocyte globulin are sometimes added to help modulate the interaction of T and B cells. Studies assessing the best treatment strategy for AMR are currently in progress.

Patients with recurrent rejection are particularly challenging to manage. A recent study by Kirklin et al. (56) has shown that the technique of photopheresis may reduce the risk of subsequent hemodynamic compromise rejection and/or death from rejection when initiated for patients with high rejection risk. Total lymphoid irradiation has also been shown to decrease the chances of subsequent rejection but may be associated with a greater risk of lymphoproliferative disorders (57).

The Changing Face of Immune and Functional Monitoring

Current immune monitoring of cardiac transplants is imperfect and revolves around the use of the endomyocardial biopsy, drug level monitoring, and echocardiography. Although this strategy has proven to be very useful, many patients still present with rejection, infection, or drug toxicity despite having the desired level of immunosuppression. Although endomyocardial biopsy is the time-honored gold standard for the diagnosis of rejection, its value may be limited by significant interobserver variability, sampling error, and the difficulty in interpreting nodular endocardial infiltrates (Quilty lesions) (36,58). There is also a wide variability in frequency and duration of surveillance endomyocardial biopsy, with most centers now limiting routine endomyocardial biopsies to <5 years (59).

An ideal immune monitoring strategy would be noninvasive, reliably allow discrimination between the presence and absence of rejection, and detect a state of overimmunosuppression. Such a strategy does not currently exist. A comprehensive monitoring strategy will most probably rely on a combination of multiple monitoring tools. These monitoring tools may include: 1) current invasive biopsy with histopathology; 2) monitoring of graft function with imaging modalities and B-type natriuretic peptide (BNP); 3) drug level monitoring; 4) genomic markers of rejection; 5) donor-specific antibodies monitoring; and 6) direct immune function assays (Table 3).

In the last 20 years, many studies have demonstrated that abnormal diastolic parameters of allograft function represent sensitive, although less specific, markers of cellular rejection (60,61). In a recent study, Dandel et al. (60) have shown that a >10% change in maximal systolic or diastolic tissue Doppler velocity of the posterior wall of the left ventricle was a sensitive and specific marker of cellular rejection (grade ≥2 in the previous classification). Validation of these findings is currently underway in several institutions. Elevation in BNP was also associated with cellular rejection in several studies, although a cutoff value with clear discriminant capacity has not been determined (62). Experience from the echocardiography literature suggests that dynamic changes in BNP may prove to be more valuable than absolute values.

In clinical practice, drug monitoring of CNIs, mycophenolate mofetil, and proliferation signal inhibitors is usually based on trough drug levels. Although logistically more difficult, several studies have shown that peak measurements

Table 3	Immune and Functional Monitoring of Heart Transplant Recipients	
Monitoring Tool	**Type**	**Value**
Endomyocardial biopsy	Histology and immunohistochemistry	Time-honored gold standard for the diagnosis of rejection; disadvantage of being invasive and susceptible to sampling errors and variability in interpretation
Drug monitoring and pharmacogenomics	Drug level or AUC	Trough levels are usually monitored for practical reasons although peak levels usually correlate better with AUC; gene polymorphisms of CYP3A5 and MDR1 correlate with calcineurin inhibitor levels
Functional monitoring	Diastolic parameters	Moderate correlation with significant rejection
	Tissue Doppler	Δ tissue Doppler systolic velocities are sensitive although less specific for the diagnosis of significant rejection
	BNP	Correlates with significant rejection; no specific threshold has good discrimination capacity
Genomic markers of rejection	AlloMap* gene expression profiling test	Sensitive marker for cellular rejection although lower specificity; not validated for AMR
T cell functional assays	1) ImmuKnow	Marker of T cell activation, currently under validation in heart transplantation
	2) Elispot	Marker of cytokine-producing T cells; currently under validation
Antibody monitoring	DSA	The presence of DSA has been associated with an increased risk of rejection and allograft vasculopathy

*XDx, Brisbane, California.
AMR = antibody-mediated rejection; AUC = area under the curve; BNP = B-type natriuretic peptide; DSA = donor-specific antibodies.

of drug levels of medication may better reflect the area under the curve of immunosuppressive drugs (63–65). More comprehensive pharmacokinetics may also allow the identification of inconstant absorbers, which could lead to further refinement in drug dosing (63).

Gene expression profiling (GEP) is also bringing new insight into the mechanisms involved in rejection (66–68). Genes that are activated during acute cellular rejection involve a wide range of pathways, including T cell activation and trafficking, natural killer-cell activation, stem cell mobilization, hematopoiesis, alloimmune recognition, and steroid responsiveness (67,68). Gene expression profiling may also be useful for rejection surveillance in heart transplant recipients. In the CARGO (Cardiac Allograft Rejection Gene Expression Observation) study, a multigene algorithm based on the expression of 20 genes (11 informative, 9 control genes) was developed and validated. The algorithm weighs the contribution of each gene and results in a score ranging from 0 to 40, with scores below threshold indicating a very low likelihood of moderate-to-severe acute cellular rejection on endomyocardial biopsy (ISHLT grade ≥3A/2R). In the CARGO study, using a threshold of 20, the test had a sensitivity for rejection of 84% (95% confidence interval: 66% to 94%) and the specificity was 38% (95% confidence interval: 22% to 56%) (66,68). The threshold of the test was later increased to 34 to improve its sensitivity. This test has not yet become a major part of clinical practice because further information is needed to assess the safety of routine GEP instead of biopsies (ongoing IMAGE [Invasive Monitoring Attenuation Through Gene Expression]

study) (68). Also, importantly, a gene expression profile that distinguishes AMR from the nonrejecting state has yet to be developed.

Direct immune assays that monitor antibody production and T cell function are also finding their way into clinical practice (6,69,70). At this time, however, no current test is both practical and specific enough to predict under- or overimmunosuppression (71). The detection of anti-HLA donor-specific antibodies has been associated with an increased incidence of early and severe allograft rejection and with the late development of cardiac allograft vasculopathy and decreased survival (6,72,73). The importance of non-HLA antibodies is also being increasingly recognized (6). Although HLA sensitization is a well-recognized risk factor for worse outcomes, the benefit of treating hypersensitized patients with normal graft function is at this time not clearly established. A recent assay of T cell function has also been recently introduced (ImmuKnow, Cyclex Inc., Columbia, Maryland). The assay measures the amount of adenosine triphosphate production by CD4+ T cells isolated from whole blood and stimulated by phytohemagglutinin. In an observational study, transplant patients with rejection had, on average, higher values, while those without rejection had lower values. A recent prospective study presented by Jon Kobashigawa at the ISHLT annual meeting (74) suggested that ImmuKnow levels are associated with rejection or infection risk. Future prospective studies are, however, needed to assess the value of ImmuKnow and other functional T cells assays in heart transplantation (70).

Transplant Allograft Vasculopathy

Transplant allograft vasculopathy represents the most common cause of late graft failure. Beyond the first year, transplant vasculopathy and malignancy are the 2 most important causes of death (5). Significant allograft vasculopathy, defined angiographically by a diameter stenosis greater than 50%, is found in approximately 30% to 50% of patients at 5 years (5,7). Compared with atherosclerotic coronary artery disease, allograft vasculopathy is usually characterized by diffuse intimal hyperplasia that may affect the epicardial vessels as well as the microcirculation in a longitudinal and concentric fashion (7,75–77). Plaque rupture is uncommon in allograft vasculopathy because of its usually diffuse and hyperplasic nature (7,75–77).

Understanding of allograft vasculopathy has progressed significantly in the last 10 years, although the exact pathophysiological mechanisms involved are still incompletely understood (7,76,77). Several immune and nonimmune risk factors have been identified. Nonimmune risk factors include hyperlipidemia, hypertension, diabetes mellitus, hyperhomocysteinemia, older donor age, and explosive etiology of donor brain death (5,78,79). Immune risk factors include HLA donor/recipient mismatches (especially HLA DR mismatches), recurrent cellular rejection, and AMR (33,61,78). The role of viral infections, especially cytomegalovirus infection, in the progression of allograft vasculopathy is also being increasingly recognized (80). Recent studies have shown that patients with cytomegalovirus infection, whether symptomatic or not, more frequently have allograft vasculopathy, which also may be more severe (80). Recent studies also suggest that donor and recipient hepatitis B and donor hepatitis C may be associated with an accelerated form of allograft vasculopathy (79).

Intravascular ultrasound is playing a greater role in the diagnosis and follow-up of allograft vasculopathy (79,81). By intravascular ultrasound criteria, allograft vasculopathy is usually defined as an intimal thickness >0.5 mm. Rapid progression of intimal thickness of more than 0.5 mm during the first year is a powerful predictor of all-cause mortality, myocardial infarction, and later angiographic abnormalities (81). Management of allograft vasculopathy focuses on the aggressive management of risk factors such as hyperlipidemia and the use of proliferation signal inhibitors such as sirolimus, which has been shown in a small study to decrease the progression of allograft vasculopathy (48,82). Statin therapy has also been recently shown to have sustained survival benefits at 10 years associated with a decrease in allograft vasculopathy (83,84). Although antiplatelet agents are commonly used, their efficacy has never been clearly established. Percutaneous revascularization of allograft vasculopathy is often considered for focal lesions, but the benefits of the procedure are limited by the diffuse nature of the disease (85). Retransplantation is also considered in selected patients with severe allograft vasculopathy.

The Changing Face of Infections in Heart Transplantation

Infection remains an important cause of mortality after heart transplantation (5,86). In general, the risk of infection changes over time in a somewhat predictable pattern (87). Infections in the early period post-transplant (<1 month) are mainly associated with technical or nosocomial factors; infection between 1 and 6 months are often associated with opportunistic organisms or activation of latent infection; infections after 6 months are more often community acquired (87). Several factors are contributing to the changing face of infection in solid organ transplantation: 1) the introduction of bacterial and viral prophylaxis (most often with trimethoprim-sulfamethoxazole and valgancyclovir); 2) early withdrawal of corticosteroids; 3) the emergence of more effective antifungal agents; and 4) the emergence of resistant strains of bacteria and viruses. The major effects of bacterial and viral prophylaxis have been the significant decrease in pneumocystis pneumonia infection, infection with herpesviruses (e.g., cytomegalovirus), as well as a decrease in infections with listeria, nocardia, and toxoplasmosis. The survival of patients with invasive aspergillus has also improved with the introduction of echinocandins (e.g., caspofungin) and new azoles (e.g., voriconazole or posiconazole) (88). In the future, more sensitive microbiological assays and better immune monitoring tools will hopefully continue to decrease the mortality of infectious complications in solid organ transplant recipients (87).

The Changing Face of Malignancies

Malignancies represent the leading cause of death among long-term survivors and equals cardiac allograft vasculopathy as a cause of death in recipients who live longer than 5 years (5). The 2 most important malignancies are post-transplant lymphoproliferative disorders and aggressive skin cancers. Solid organ recipients at high risk for post-transplant lymphoproliferative disorder include Epstein-Barr virus seronegative patients, especially if they receive a seropositive donor, nonrenal transplants, more aggressive maintenance immunosuppression, and younger patients (89). There also exists a probable link between lymphoproliferative disease and OKT3 induction therapy (42). The incidence of skin cancer is expected to increase with the increasing age of recipients. Major advances in the treatment of cancer in heart transplant recipients include the introduction of proliferation signal inhibitors, which slow the progression of and may even lead to the regression of some malignancies, as well as advances in the treatment of lymphomas (such as rituximab) or invasive skin cancers (such as Mohs micrographic surgery) (42,89).

The Changing Face of RF

The incidence of RF after heart transplantation is also expected to increase as the recipient population becomes older and sicker. Severe RF after heart transplantation is a risk factor for both short- and long-term mortality (5). Several recent studies have established risk factors associated with both acute and chronic RF. Boyle et al. (90) recently described risk factors for acute RF after heart transplantation. In their large retrospective study, acute RF requiring dialysis occurred in 5.8% of patients and was associated with increased mortality and length of hospital stay (89). Multifactorial analysis identified pre-transplant creatinine, insulin-requiring diabetes mellitus, hypoalbuminemia, and duration of bypass as predictive of severe acute RF. The most common cause of chronic RF after heart transplantation is CNI toxicity. Other causes include graft failure, nephrotoxic antimicrobials, or medication interactions that inadvertently increase the levels of CNIs. Established risk factors for chronic RF include increasing recipient age, diabetes mellitus, pre-transplant RF, post-operative acute RF, and HLA hypersensitization (91,92). The CNI-free regimens combining sirolimus and mycophenolate mofetil have recently been shown to improve renal function without increasing the risk of rejection when initiated several years after transplantation (52,53).

Tolerance Induction

Progress toward achieving clinical tolerance, the holy grail of transplantation, has been slow but steady over the last 4 decades (93). Tolerance refers to a state of permanent immunological acceptance of the graft (in this case the heart) without the need for ongoing immunosuppression beyond the peri-transplantation period (94). Tolerance also implies preserved immunological response to new or previously encountered immune challenges (94). Achieving tolerance would considerably reduce the complications associated with chronic immunosuppression. One of the ongoing difficulties in studying tolerance at this time is the lack of specific markers of tolerance (70). Also, importantly, inducing tolerance in heart transplantation may be inherently different than inducing tolerance in kidney transplantation. This may be related to differences in the number of HLA mismatches or different intensity or type of alloimmune response between different organs (70,94,95). Successful induction of clinical tolerance in renal transplantation has mainly relied on concurrent stem cell transplantation and the achievement of mixed bone marrow chimerism (96,97). Because heart transplantation usually involves no HLA matching, such chimerism induction would require potent ablation of the recipient bone marrow, significant radiation exposure, and ongoing immunosuppression (94). Therefore, at this time clinical trials of mixed chimerisms in heart transplantation do not seem justified. Promising approaches involving peripheral tolerance induction in heart transplantation using monoclonal antibodies or fusion proteins to inhibit costimulation and T cell activation are currently being studied (94).

Conclusions

Heart transplantation continues to offer patients with end stage heart failure a chance for a better quality and length of life. Over the last 4 decades, a better understanding of the alloimmune response has led to improved monitoring of rejection and the development of better immunosuppressive regimens. In the future, advances in immunosuppression protocols, organ preservation, and the use of more specific immune monitoring tools are likely to lead to significant improvements in outcomes. Maybe one day, achievement of the holy grail of transplantation, immune tolerance, will eventually open the door to normal lives and life spans for all transplant recipients.

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