

Transplantation Overview

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I. Why do we need cardiac transplantation?

Congestive Heart Failure (CHF) is a major cause of morbidity and mortality in the U.S, as evidenced by the following data: 1) currently, >5,000,000 in the U.S. have CHF, 2) CHF is the leading Medicare discharge diagnosis in the elderly, and 3) >400,000 new cases of CHF are diagnosed annually in U.S. It was estimated in the early 1990's that as many as 40,000 could benefit from heart transplantation per year in U.S. might benefit from cardiac transplantation for end-stage CHF. However, primarily due to limitation in the number of available donor organs, the number of transplants performed yearly at

the approximately 300 cardiac transplant centers worldwide total <4,000. In addition, cardiac transplantation is an incredibly resource-intensive therapy that requires a high level of medical sophistication. Thus, much of the demand for treatment of advanced CHF must be met through advances in pharmacological and mechanical device therapy. Nevertheless, because cardiac transplantation remains the gold standard for treatment of end-stage CHF, we perform as many as we possibly can.

II. Background on Solid Organ and Cardiac Transplantation.

You may be interested in some milestones in solid organ transplantation in the US and Canada. These are listed in **Table 1**. Also, **Table 2** lists the longest-surviving solid organ transplants and **Table 3** lists the youngest surviving solid organ transplant recipients (both as of 6/5/03).

Table 1. Transplant Milestones in the U.S. and Canada

1954	First successful kidney transplant* Dr. Joseph E. Murray; Brigham & Women's Hospital, Boston, MA
1966	First simultaneous pancreas/kidney transplant Drs. Richard Lillehei, William Kelly University of Minnesota, Minneapolis, MN
1967	First successful liver transplant* Dr. Thomas Starzl; University of Colorado, Denver, CO
1968	First isolated pancreas transplant Dr. Richard Lillehei, University of Minnesota, Minneapolis, MN
1968	First successful heart transplant Dr. Norman Shumway, Stanford University Hospital, Stanford, CA
1981	First successful heart-lung transplant Dr. Bruce Reitz, Stanford University Hospital, Stanford, CA.
1983	First successful single lung transplant Dr. Joel Cooper, Toronto General Hospital, Canada
1986	First successful double lung transplant* Dr. Joel Cooper, Toronto General Hospital, Canada
1989	First successful living-related liver transplant Dr. Christoph Broelsch, University of Chicago Medical Center, Chicago, IL
1990	First successful living-related lung transplant Dr. Vaughn A. Starnes, Stanford University Medical Center, Stanford, CA

***This transplant was the first of its kind in the world**

Table 2. Longest-Surviving Solid Organ Transplants

Organ	Date of Tx	Age at Tx	Years of Continued Function	Transplant Center
Kidney (LRD)	1/31/63	38	38 yrs, 11 mos	University of Colorado Denver
Kidney (CAD)	3/30/66	19	35 yrs, 9 mos	University of Minnesota Minneapolis
Pancreas	5/21/83	33	18 yrs, 7 mos	University of Minnesota Minneapolis
Liver	1/22/70	3	31 yrs, 11 mos	University of Colorado Denver
Heart	8/30/78	20	23 yrs, 4 mos	Stanford University
Heart-Lung	11/21/83	26	18 yrs, 1 mo	University of Pittsburgh
Lung(Single)	8/2/87	46	14 yrs, 3 mos	The Toronto Hospital
Lung(Double)	10/8/90	39	17 yrs, 2 mos	Stanford University

Table 3. Youngest-Surviving Solid Organ Transplant Recipients

Organ	Date of Tx	Age at Tx	Years Cont'd Function*	Transplant Center
Kidney (LRD)	6/10/82	6 months	18 yrs, 6 mos	University of Minnesota Minneapolis
Kidney (CAD)	3/11/88	4 months	13 yrs, 9 mos (Cr = 1.0)	Huddinge Hosp-Sweden
Pancreas	(no data available)			
Liver	6/12/92	12 days	9 yrs, 6 mos	University of Chicago
Heart	10/16/87	3 hours	14 yrs, 2 mos	Loma Linda University Hospital
Heart-Lung	1/1/93	3 years	8 yrs, 11 mos	U. N. Carolina-Chapel Hill;
Lung (Single)	(no data available)			
Lung (Double)	3/11/94	2 months	7 yrs, 9 mos	Washington University St Louis

Table 4 lists the number of U.S. Transplant Programs certified by the United Network for Organ Sharing (UNOS), which is the not-for-profit organization that contracts with the Center for Medicare and Medicaid Services (CMS) to run the organ distribution scheme in the U.S. **Table 5** shows the number of each organ transplant type performed in U.S. in 2001.

Table 4. UNOS-certified Organ Transplant Programs

Kidney Transplant Programs	242
Liver Transplant Programs	120
Pancreas Transplant Programs	138
Panreas Islet Cell Transplant Programs	34
Intestine Transplant Programs	38
Heart Transplant Programs	140
Heart-Lung Transplant Programs	81
Lung Transplant Programs	75
Total	868

Table 5. Number of Transplants in US by Organ

Kidney Only (5,293 were living-related donors)	14,152
Liver	5,177
Pancreas Only	468
Kidney-Pancreas	884
Intestine	112
Heart Only	2,202
Heart-Lung	27
Lung	1,054
Total	24,076

Interestingly, the success of organ transplantation in general, as well as of cardiac transplantation in particular, has increased substantially over the past decade, probably due to a combination of the introduction of cyclosporine in 1979, and to improved operative and post-operative care. Currently,

according to data from the Registry of the International Society for Heart and Lung Transplantation (ISHLT), the average survival of a cardiac transplant patient is 9.1 years; in other words, the average survival at 9.1 years post-transplant is 50%. In contrast, 10 year survival for the UW Cardiac Transplant Program patients is \cong 75-80%.

III. Selection of Candidates for Cardiac Transplantation.

In general, patients are selected for cardiac transplantation if they: 1) have CHF that is sufficiently advanced that their survival is likely to be greater with cardiac transplantation than without it, and 2) do not have significant contraindications that would either limit their ability to survive the transplant operation or to tolerate or comply with the requisite, rigorous medical follow-up required following transplantation. **Table 6** lists the tests required as a part of the standard cardiac transplantation evaluation for the UWMC cardiac transplant program:

Table 6. Elements of the UWMC Cardiac Transplant Evaluation.

Laboratories:		
<input type="checkbox"/> CBC with diff and plt <input type="checkbox"/> Coagulation Screen <input type="checkbox"/> Comprehensive Metabolic Panel <input type="checkbox"/> Sedimentation Rate <input type="checkbox"/> ANA Reflexive Panel <input type="checkbox"/> SPEP and UPEP <input type="checkbox"/> Uric Acid	<input type="checkbox"/> Iron Studies <input type="checkbox"/> Thyroid Studies <input type="checkbox"/> Prostate Specific Antigen <input type="checkbox"/> Fasting Lipid Panel <input type="checkbox"/> Blood Type <input type="checkbox"/> Urinalysis <input type="checkbox"/> 24 h urine protein <input type="checkbox"/> Urine albumin/creatinine ratio	<input type="checkbox"/> Hepatitis A, B and C Antibody Screens <input type="checkbox"/> HSV Antibody <input type="checkbox"/> EBV Antibody <input type="checkbox"/> VZV Antibody <input type="checkbox"/> HIV Screen <input type="checkbox"/> RPR Antibody Screen <input type="checkbox"/> Rubella and Measles Antibody Screens <input type="checkbox"/> Toxoplasma IgG and IgM
Diagnostic Studies:		
<input type="checkbox"/> Right Heart Catheterization <input type="checkbox"/> Echocardiogram <input type="checkbox"/> 12-lead ECG <input type="checkbox"/> Vascular Studies (Carotid and LE Arterial) in patients with DM, \uparrow lipids, PVD or CAD	<input type="checkbox"/> PFTs (Spirometry, Volumes, MVV, DLCO) <input type="checkbox"/> PA and Lateral CXR <input type="checkbox"/> PPD with Controls (Mumps, Candida, Trichophyton)	<input type="checkbox"/> Stool Guaiac X3 <input type="checkbox"/> Pap Smear <input type="checkbox"/> Mammogram
Consults:		
<input type="checkbox"/> Social Work Evaluation <input type="checkbox"/> Financial Counseling (UWMC Financial Services)	<input type="checkbox"/> Dental Evaluation (private or UWMC dentist) <input type="checkbox"/> Nutrition Evaluation	<input type="checkbox"/> Patient Education (UWMC Transplant Coordinators)

Significant contraindications to heart transplantation include:

- Advanced age (>70)
- Irreversible hepatic, renal or pulmonary dysfunction
- Severe peripheral or cerebrovascular disease
- Insulin-requiring DM with end-organ damage
- Active infection

- Recent cancer with uncertain status
- Psychiatric illness
- Poor medical compliance
- Systemic disease that would limit survival or rehabilitation
- Pulmonary HTN (PVR > 6 Wood units or >3 Wood units after vasodilator)

IV. Adult Cardiac Transplantation Candidate Status

UNOS has developed criteria for listing patients for cardiac transplantation based on their severity of illness. In general, the idea is that the most ill patients (those with the highest short-term mortality) are the most likely to have a survival benefit from transplantation. There are 3 active statuses (1A, 1B and 2) and one status for patients who are unsuitable to receive an organ at present, either due to intercurrent illness or, occasionally, to significant improvement in their clinical status. **Table 7** lists the listing criteria for each status

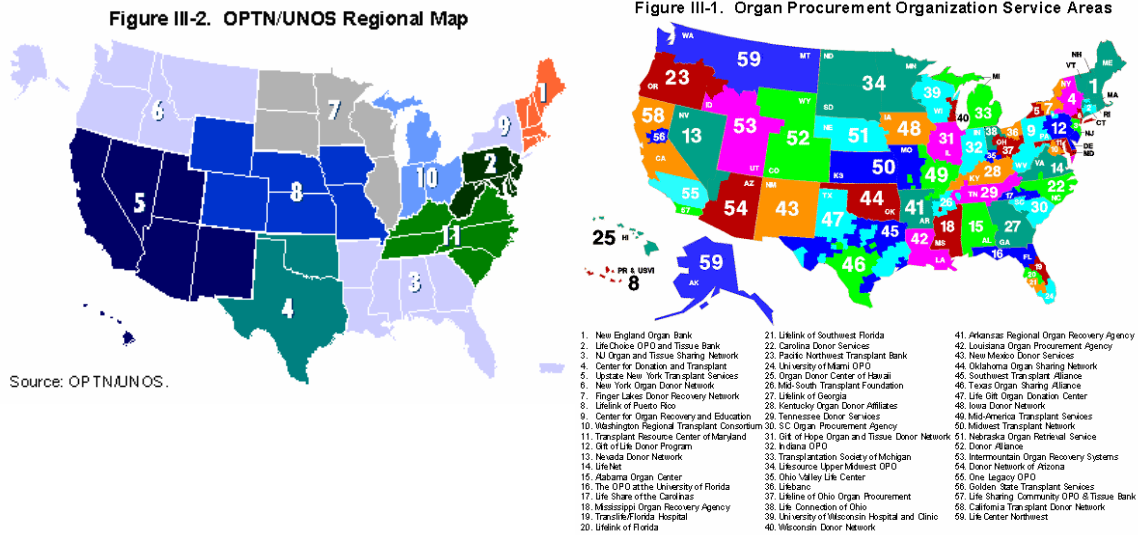
Table 7. UNOS Cardiac Transplant Status Listing Criteria.

UNOS Status	Criteria
1A	Inpatient + one of the following: <ul style="list-style-type: none"> • MCS (VAD ≤ 30d; TAH; IABP; ECMO) • MCS > 30d + signif. Device-related complication • mechanical ventilation • continuous infusion of 1 high-dose or multiple inotropes • life expectancy < 7 d without transplant
1B	One of the following: <ul style="list-style-type: none"> • VAD > 30 d • continuous infusion of IV inotropes • justified exceptional case
2	Does not meet status 1A or 1B criteria
7	Temporarily unsuitable to receive organ

MCS: mechanical circulatory support, VAD: ventricular assist device; TAH: total artificial heart, IABP: intraaortic balloon pump, ECMO: extracorporeal membrane oxygenation

To manage distribution of potential donor organs, UNOS has designated 11 UNOS Regions and 59 Organ Procurement Organization Service Areas. Our program is located in Region 6, which has the largest geographic area of any of the 11 Regions, but which also has the smallest population. Within Region 6, we are in Organ Procurement Organization (OPO) Service Area 59, which is serviced by LifeCenter Northwest. Coordinators from LifeCenter Northwest are called when a potential donor becomes available and evaluate the potential donor's organs for suitability for transplantation. If a donor heart appears suitable for transplantation, the organ is first offered to cardiac transplantation programs in the OPO Service Area (in our area, this means UWMC or Sacred Heart in Spokane). Patient priority for organs is determined by 1) ABO type, 2) body size (generally the recipient weight should be within 20% of the donor weight), 3) UNOS Status and 4) for patients in a given UNOS Status, time on the list at that status. **Figure 1** shows the UNOS Regional Map (**Fig. 1, left**) and OPO Service Area Map (**Fig. 1, right**).

Figure 1. UNOS Regional and OPO Service Area Maps.



Unfortunately, the number of deceased donors has increased by only about 25% in the past 10 years (**Figure 2**). In contrast, the number of living related donors (primarily kidney and liver) has increased more dramatically over that same time period (**Figure 2**). The 25% increase in deceased donors has resulted primarily from an increased acceptance of older donors, as evidenced by the increased average age of deceased donors (**Figure 3**).

Figure 2. Deceased and Living Donors, 1992-2001

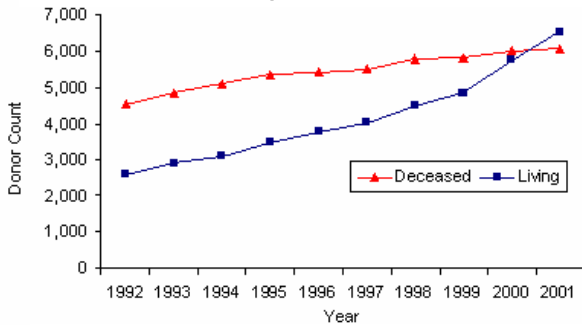


Figure 3. Median Age of Deceased Organ Donors and U.S. Population

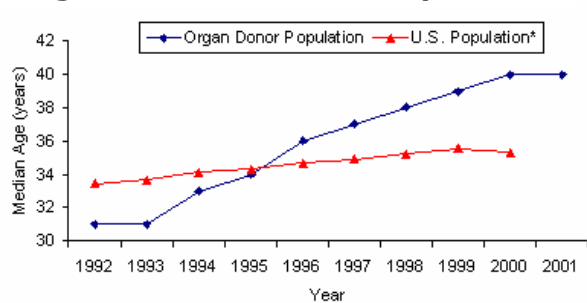
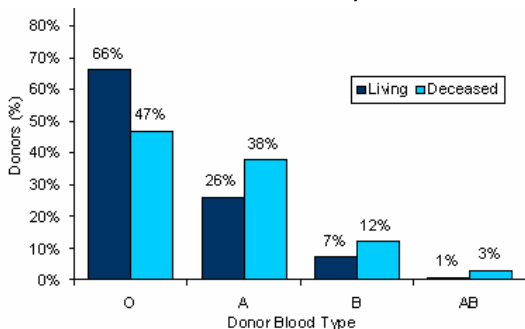
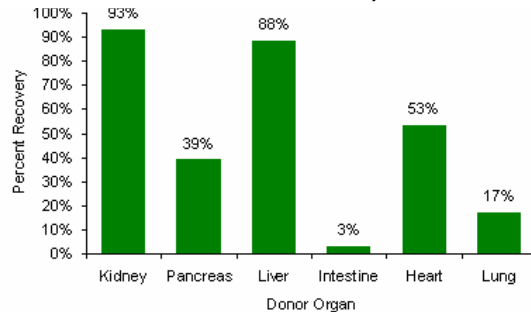


Figure 4. Donor Blood Types, by Living Or Deceased Donor, 2001



Source: 2002 OPTNSRTR Annual Report, Tables 2.1, 2.8.

Figure 5. Organ Recovery Rates From Deceased Donors, 2001



Source: 2002 OPTNSRTR Annual Report, Tables 3.1, 3.3, 3.4, 3.6, 3.7, 3.9, 3.10, 3.12, 3.13, 3.15, 3.16, 3.18.

Figure 4 shows the distribution of donor blood types for living and deceased organ donors, while **Figure 5** shows the rates for recovery of different organs from deceased donors. Note that hearts are procured from only 53% of deceased donors, and lungs from only 17%. In contrast, recovery rates for

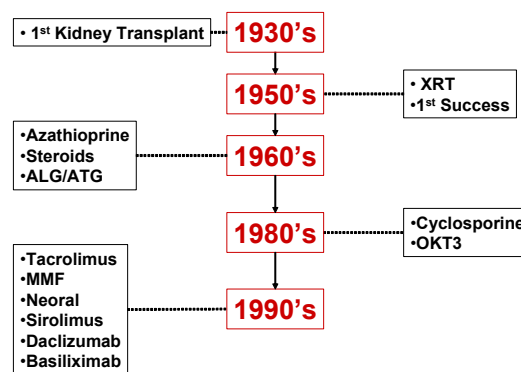
kidneys and livers are much higher, primarily due to the fact that these organs can tolerate much longer periods of ischemia and are not as likely to have significant impairment due to prior disease (e.g., CAD) or trauma (e.g., RV contusion) as is the heart.

V. Immunosuppression.

The development of effective strategies to prevent rejection represented the key to the development of transplantation as an effective therapy for end-stage organ dysfunction. Originally, it was hoped that strategies could be developed by which “graft tolerance” could be achieved. “Graft tolerance” can be defined as development of graft acceptance due to alteration in the donor organ so that it is recognized as self by the recipient. Unfortunately, there currently is no strategy that achieves graft tolerance to any clinically useful degree.

The alternate strategy to prevent rejection is “immunosuppression” in which the recipient’s immune system is altered so that it cannot respond to foreign tissue. **Figure 6** summarizes some of the milestones in the development of immunosuppression; the strategies in current clinical use will be discussed in more detail in a later section.

Figure 6. History of Immunosuppression



XRT= radiation therapy, ALG/ATG=anti-lymphocyte/anti-thymocyte globulin, OKT3=monoclonal anti-CD3 antibody, MMF=mycophenolate mofetil

Rejection is primarily mediated through recognition by the immune system of one or more Human Leukocyte Antigens (HLA) on the donor organ. HLA are a cluster of genes on chromosome 6 that encode for cell-surface proteins that are antigens (targets) for T-cells. Each individual has 6 major HLA antigens, but across the population, there are a large number of different types for each HLA antigen. In renal transplantation, both recipients and potential donors undergo typing to determine the specific identity of each of their 6 major HLA antigens, and attempts are made to ensure that the donor and recipient share as many of their respective HLA types as possible.

In cardiac transplantation, differences (mismatches) in HLA types appear to have much less of an effect on graft acceptance; for this and other reasons, HLA matching is not routinely done for cardiac transplantation in the U.S. However **hyperacute rejection** can arise if the recipient has pre-formed, complement-fixing antibodies against HLA antigens of the donor organ. Hyperacute rejection results in severe graft dysfunction and is usually fatal. Patients typically are immunized against foreign HLA antigens (“alloimmunized”) either through pregnancy or transfusion of whole blood, platelets or packed red blood cells (pRBCs). The risk of alloimmunization from pRBCs can be reduced, though not eliminated, if leukocyte-reduced pRBCs are used.

To assess the likelihood of the presence of preformed anti-HLA antibodies, serum from potential cardiac transplant recipients is screened using the PRA (**Panel of Reactive Antibodies) test**. In the PRA test, recipient serum is exposed to T lymphocytes and to B lymphocytes from a pool of 40-50 random blood donors. If the recipient's serum contains any complement-fixing, and therefore cytolytic, antibodies against HLA antigens present on the lymphocytes, the lymphocytes are lysed. The results are reported as the percentage of positive reactions/total # donors screened for both the T lymphocyte and B lymphocyte assays, and are very useful in identifying patients who may be at risk for hyperacute rejection due to alloantibodies. For example, if the T- and B-lymphocyte PRAs are, respectively 0% and 0%, then the risk of hyperacute rejection is very low.

If a recipient has an elevated PRA is elevated (usually >10%) has not had 2 serial PRA tests, or has recently received blood products, then a **Prospective Cross-Match** is required by our program. In a prospective cross-match recipient serum is directly tested against donor lymphocytes that have been isolated from the prospective donor's blood or harvested lymph nodes. If the cross-match is positive (the potential recipient's serum contains cytolytic antibodies against the potential donor's T- or B-lymphocytes) then the donor organ is not offered to that recipient. In one study, in which cross-matches were performed *following* cardiac transplantation (retrospective cross-matches), a positive B-lymphocyte cross-match was associated with a 40% 6-month mortality, and a positive T-lymphocyte cross-match was associated with a 70% 6-month mortality.

General Immunosuppressive Strategies.

Table 8 shows the current protocol for Induction and Maintenance immunosuppression in the UWMC Cardiac Transplant Program.

Table 8. UWMC Immunosuppression Protocol.

	Steroid	Azathioprine (Imuran®) or MMF (CellCept®)	Tacrolimus (Prograf®)	ATG
Pre-op	Methylpred 500-1000 mg IV X1	4 mg/kg IV <input type="checkbox"/> 1 mg/kg IV if on allopurinol <input type="checkbox"/> 2 mg/kg IV if WBC<4000	NONE	NONE
Intra-op	Methylpred 500-1000 mg IV X1 After CPB	NONE	NONE	Day 0: 1.5 mg/kg when bypass clamp removed
Post-op Days 0-1	Methylpred 125 mg IV q8h X3	MMF 1 gm PO or IV q12 h; hold for WBC<4000	NONE	Day 1: 1 mg/kg at 21:00 (+Tyl 650 mg/Ben 50 mg IV)
Post-op Day 2	Pred 0.15 mg/kg/dose bid	Continued	If Cr<2 and taking PO, 1 mg PO bid	NONE
Post-op Day 3	Continued	May ↑ to 1.5 gm PO bid if tolerated and WBC>4000	If Cr<2, ↑ tacrolimus; goal level is 12-15 ng/mL for Months 0-3	1 mg/kg at 21:00 (+Tyl 650 mg/Ben 50 mg IV)
Post-op Day 4	Continued	Continued	Continued	NONE
Post-op Day 5+	Continued X6 weeks, then taper	Continued	Continued	1 mg/kg at 21:00 (+Tyl 650 mg/Ben 50 mg IV)

Immunosuppression can be divided into two phases, the “Induction” Phase (i.e., peri- and immediate post-transplant immunosuppression and the “Maintenance” Phase. **In the “induction” phase**, the patient is given 3 classes of agents: 1) anti-thymocyte globulin, a preparation containing complement-fixing antibodies that recognize and lyse T-lymphocytes, 2) high-dose corticosteroids, and 3) either azathioprine or mycophenolate mofetil, which inhibit T-lymphocyte proliferation by inhibiting DNA synthesis. **In the “maintenance” phase**, 3 drugs also are given to prevent rejection: 1) prednisone, dosed initially at .15mg/kg bid, but then weaned over the subsequent 6 months, hopefully to off, 2) an inhibitor of purine metabolism, either mycophenolate mofetil (CellCept®) at 1,000-1,500 mg bid or azathioprine (Imuran®) at 2 mg/kg qPM, and 3) a calcineurin inhibitor, either cyclosporine or tacrolimus (Prograf®), which inhibit the production of interleukin-2 (IL-2).

Calcineurin Inhibitors:

The cornerstone of current immunosuppressive regimens is the use of an agent that inhibits the production of interleukin-2 (IL-2) by the inhibition of an intracellular signaling molecule, calcineurin. The 2 commonly available calcineurin inhibitors are cyclosporine (Sandimmune®, Neoral®, Gengraf®) and tacrolimus (Prograf®, also often referred to by its investigational drug name, FK-506). General advantages of cyclosporine over tacrolimus include: 1) lesser insulin resistance/diabetes and 2) a longer track record. In contrast, tacrolimus has the perceived advantages of: 1) lesser effect on hypertriglyceridemia, 2) probably more effective immunosuppression, 3) less hypertension and 4) possibly less renal dysfunction, though this latter point is really arguable. In addition, in dyslipidemic post-transplant patients, tacrolimus has the advantage that it doesn’t interfere with bile acid sequestrants. **Table 9** compares some of the features of cyclosporine and tacrolimus.

Table 9. Calcineurin Inhibitors.

Drug	MOA/ PK	Dosing	Side Effects	Monitoring	Drug Interactions	Cost
Cyclosporine: • Sandimmune ® • Microemulsion: Neoral ®, Gengraf ®	<ul style="list-style-type: none"> Inhib IL-2 synthesis (block calcineurin) Absorp: 30% LDL-bound Metab: P450 3A4 T ½: 8h 	Day 0: • none Day 1: 1 mg/kg/d IV if Cr <2 Day 2: 2 mg/kg/d IV Day 3: 3 mg/kg/dose bid PO IV= 1/3 PO	<ul style="list-style-type: none"> Nephrotox ↓ Mg, ↑ K, BP, BS, lipids (LDL) Neurotox paresthesia HUS Gum hyperplasia 	Labs: • BUN/Cr, K, Mg, lipid, LFT, BS Levels: (see below)	<ul style="list-style-type: none"> ↑ Levels: Erythro, Ketoconazole, Fluconazole, Diltiazem, Verapamil, Grapefruit ↓ Levels: DPH, Rifampin, PB, carbamazepine 	\$1000 /mo
Tacrolimus: • Prograf ® (FK506)	<ul style="list-style-type: none"> See above (block calcineurin) Absorp: 15% LDL-bound Metab: P450 3A4 T ½: 8h 	Induction • 0.025-0.05 mg/kg PO q12h (IV: 0.05-0.1 mg/kg/d) Maint: • 0.025 mg/kg PO q12h IV=1/3 PO	<ul style="list-style-type: none"> Nephrotox ↓ Mg, ↑ K, BP, BS, lipids (LDL) Neurotox Paresthesia Alopecia Anorexia 	Labs: • BUN/Cr, K, Mg, lipid, LFT, BS Levels: (see below)	<ul style="list-style-type: none"> ↑ Levels: Erythro, Ketoconazole, Fluconazole, Diltiazem, Verapamil, Grapefruit ↓ Levels: DPH, Rifampin, PB, carbamazepine 	\$500-1000/mo

Anti-thymocyte/anti-lymphocyte Preparations:

These consist of either polyclonal antisera or mouse monoclonal antibodies that provide very effective short-term immunosuppression by binding to T lymphocytes, fixing complement and thereby lysing T lymphocytes. Available preparations include: 1) rabbit anti-thymocyte globulin (RATG), which is administered peri-operatively to prevent early rejection and also is the first line agent in our program for treatment of severe rejection with hemodynamic compromise; note that there is a high incidence of thrombocytopenia with this agent, and 2) OKT3, a commercially-available mouse monoclonal antibody directed against a subunit of the common T-lymphocyte receptor, which is used rarely in our program, primarily in patients that have developed antibodies to rabbit proteins (e.g., RATG). **Table 10** compares OKT3 and RATG.

Table 10. Anti-thymocyte Preparations.

Drug	MOA/ PK	Dosing	Side Effects	Monitoring	Drug Interactions	Cost
Muromonab: • Orthoclone OKT3®	<ul style="list-style-type: none"> Blocks T cell receptor by binding to CD3 T $\frac{1}{2}$: 18h 	Induction: <ul style="list-style-type: none"> 2.5-5 mg IV qd X 5-14 d Severe Rejection: 5-10 mg IV qd X 10-14 d Premeds: <ul style="list-style-type: none"> Steroid, Benadryl, Tylenol 	<ul style="list-style-type: none"> Fever, chills, HA, diarrhea, HTN, aseptic meningitis, nasal congestion 	Labs: <ul style="list-style-type: none"> CD3 count (<0.01) OKT3 antibodies checked prior to second course 	<ul style="list-style-type: none"> None known 	\$1000/ 5 mg dose
Anti-thymocyte globulin (ATG): • Thymoglobulin® (rabbit polyclonal Ab)	<ul style="list-style-type: none"> Binds multiple CD sites and lyses cells T $\frac{1}{2}$: 2-14 d 	Induction <ul style="list-style-type: none"> 1-1.5 mg/kg IV post-CPB 1 mg/kg Days (0, 1, 3, 5) Premed: <ul style="list-style-type: none"> Tyl, Ben 	<ul style="list-style-type: none"> ↓ WBC, RBC, Platelets Fever, chills, HA, diarrhea, SOB, HTN, hypotension, rash 	Labs: <ul style="list-style-type: none"> CBC CD3 count (<0.05) 	<ul style="list-style-type: none"> None known 	\$1250/ 100 mg dose

DNA Synthesis Inhibitors:

The two available DNA synthesis inhibitors are azathioprine (Imuran®) and mycophenolate mofetil (CellCept®), often referred to as “MMF”. The major advantage of azathioprine is its much lesser cost as compared to MMF. In contrast, MMF has the advantages that it: 1) is less likely to cause anemia, 2) is more effective as an immunosuppressant, particularly for the treatment of vascular rejection and 3) has been shown in randomized trials to be associated with a much lower risk of transplant coronary artery disease. Table 11 compares some of the characteristics of azathioprine and MMF.

Table 11. DNA Synthesis Inhibitors.

Drug	MOA/ PK	Dosing	Side Effects	Monitoring	Drug Interactions	Cost
Azathioprine: • Imuran [®] • Generic	Purine analog	Induction • 4mg/kg iv Maintenance • 2 mg/kg/d	<ul style="list-style-type: none"> • ↓ WBC, RBC, plt • Alopecia • N/V • diarrhea • pancreatitis 	Labs: • CBC: adjust based on WBC (goal >4,000)	<ul style="list-style-type: none"> • ↑ Levels with allopurinol • ↓ anticoag effect of warfarin 	\$50-100/mo
Mycophenolate: • Cellcept [®] • MMF	Inhibits rate-limiting enzyme in purine salvage pathway	Induction • 1.5 gm po/iv then 1.5 gm iv q12h Maintenance • 1 gm po bid (range 0.5-3 gm/d) • IV=PO dose	<ul style="list-style-type: none"> • ↓ WBC, RBC, plt • DIARRHEA • N/V 	Labs: • CBC Levels: • MPA 2-5 mcg/ml	<ul style="list-style-type: none"> • ↓ levels with antacids, cholestyramine, food 	\$500-750/mo

Newer immunosuppressive agents are available, in particular sirolimus and everolimus, but these currently are rarely used in this program.

VI. Rejection Surveillance:

Rejection and infection are the major early complications of cardiac transplantation. Unfortunately, patients generally do not develop symptoms related to rejection until they have developed severe ventricular dysfunction. Therefore, an important component of post-transplant management is a schedule of regular endomyocardial biopsies. This allows detection of rejection at an early stage, so that enhanced immunosuppression can be given before severe rejection has occurred. Endomyocardial biopsies are graded according to a standardized scale (**Table 12**) developed by the International Society of Heart and Lung Transplantation (ISHLT).

Table 12. ISHLT Endomyocardial Biopsy Scale.

ISHLT Grade	Alternate Description	Findings
0	“NSR” (no significant rejection)	No rejection
1A	“Focal Mild”	Focal (perivascular or interstitial) infiltrate without necrosis
1B	“Mild”	Diffuse but sparse infiltrate without necrosis
2	“Focal Moderate”	One focus only with aggressive infiltration and/or focal myocyte damage
3A	“Moderate”	A: Multifocal aggressive infiltrates and/or myocyte damage
3B	“Moderate to Severe”	Diffuse inflammatory process with necrosis
4	“Acute Severe”	Diffuse aggressive polymorphous infiltrate <u>±</u> edema, <u>±</u> hemorrhage, <u>±</u> vasculitis, with necrosis

We use a graded regimen of immunosuppressive “augmentation” in response to the biopsy findings (**Table 13**). The biopsy results also are used to guide prednisone “weaning” in the first several months post-transplant.

Table 13. Biopsy-Based Immunosuppression Management.

Descriptor (ISHLT Grade)	Response
NSR (0)	<input type="checkbox"/> Wean prednisone
Focal Mild (1A)	<input type="checkbox"/> <u>May</u> wean prednisone if hemodynamics normal <input type="checkbox"/> No prednisone change if dose \leq 10 mg/d
Mild (1B)	<input type="checkbox"/> No prednisone wean <input type="checkbox"/> If poor hemodynamics, optimize immunosuppression through 1 or more of following: <ul style="list-style-type: none"> ○ Optimize cyclosporine or tacrolimus level ○ Increase MMF or azathioprine dose
Focal Moderate (2)	<input type="checkbox"/> Probably give augmented prednisone; dose will depend on hemodynamics and biopsy trends: <ul style="list-style-type: none"> ○ Either Prednisone 50 mg/d X3d or 100 mg/d X3d, then either return to previous dose or wean to previous dose by decrease of 5 mg/d ○ REBIOPSY IN \leq2 WEEKS
Moderate (3A) or higher	<input type="checkbox"/> Without hemodynamic compromise: <ul style="list-style-type: none"> ○ Solumedrol 500-1000 mg iv daily X3d <input type="checkbox"/> With hemodynamic compromise: <ul style="list-style-type: none"> ○ Cytolytic antibody (RATG or OKT3)

Protocol for routine biopsy schedule is shown in **Table 14**.

Table 14. Routine Biopsy Schedule.

Time Post-Transplant	Biopsy Frequency
0-6 wks	Weekly
6-8 wks	Q 10 d
2-3 mo	Q 2 wk
3-4 mo	Q 3 wk
4-6 mo	Q 1 mo
6-9 mo	Q 1-1.5 mo
9-12 mo	Q 2-.5 mo
1-2 yr	Q 3-4 mo
2-3 yr	Q 4-6 mo

VII. Infections:

Infections are the other early major complication following cardiac transplantation. The incidence of infection is \cong 50% in the first 6 months following transplantation and \cong 65% in the first post-transplant year.

Early infections, occurring within the 1st month post-transplantation are generally bacterial and usually pulmonary. Mediastinitis is another serious early infection, with an incidence of \cong 0.4-0.5%

Late infections are more diverse. Bacterial sinusitis is a common minor infection. However, more serious infections, especially opportunistic infections can occur. These include infections with CMV, HSV, PCP, *Candida*, *Aspergillus*, *Nocardia*, and *Toxoplasma*. Patients are given prophylaxis with specific antimicrobials to decrease the risk of many of these infections (**Table 15**).

Table 15. Post-transplant Antimicrobial Prophylaxis.

Prophylaxis Indication	Timing	Agent/Dose
Surgical Antibiotics	until chest tubes removed	Cefazolin 1 gm IV q8h If PCN allergic, Vancomycin 1 gm IV q12h
Candidiasis	Day 0+	Nystatin 5 mL swish and swallow PO qid OR Clotrimazole 10 mg troche PO qid
Pneumocystis	Day 14+	Single-strength trimethoprim/sulfamethoxazole PO daily
Cytomegalovirus	(none if BOTH donor and recipient are CMV-negative) While NPO When taking PO	Ganciclovir 5 mg/kg IV q12h* Ganciclovir 1000 mg PO tid X3mo*
HSV/EBV	Month 4-6 (when ganciclovir discontinued) Month 6+	Acyclovir 400 mg PO tid* Acyclovir 200 mg PO tid

*Adjustment required for renal insufficiency

Table 16 shows how ganciclovir should be adjusted for renal insufficiency.

Table 16. Ganciclovir Dosage Adjustment for Renal Insufficiency.

CrCl	IV Dose (for TREATMENT of active disease)	PO Dose (for PROPHYLAXIS only)
>70	5 mg/kg q12h	1 gm tid
50-69	2.5 mg/kg q12h	500 mg tid
25-49	2.5 mg/kg q24h	500 mg bid
10-24	1.25 mg/kg q24h	500 mg qd
<10	1.25 mg/kg 3X/wk	500 mg 3X/wk

VIII. Implications of Post-Transplant Cardiac Denervation.

One major consideration in post-cardiac transplant patients is the fact that they lack sympathetic innervation to the heart. This results in: 1) β -receptor up-regulation, 2) \uparrow responsiveness to Isuprel, Levophed and, most importantly, a delayed and blunted chronotropic response to exercise.

In addition, the hearts lack resting vagal tone. This results in: 1) an elevated resting HR, 2) unresponsiveness to atropine, and 3) **inability of digoxin to block the AV node**. Therefore, to slow the ventricular response in rapid atrial fibrillation or atrial flutter, other agents must be used.

Finally, because the hearts also lack afferent nerve fibers, patients do not generally feel pain during endomyocardial biopsies and they **do not experience angina**. Occasional patients experience partial reinnervation, which can result in restored ability to sense anginal or biopsy pain.

IX. Post-transplant arrhythmias.

The most common post-transplant arrhythmia is **post-operative sinus node dysfunction**. This has an incidence in some series of as high as 10-20%. Often this will recover, but it may require temporary atrial pacing. Alternatively, sinus rate often can be increased with PO theophylline.

Resting heart rate is often increased in post-transplant patients, but if patients have **significant sinus tachycardia (HR > 120)**, consider \downarrow volume, \downarrow glucose, rejection, silent MI, adrenal insufficiency, pulmonary embolism, tamponade, or intra-abdominal catastrophe.

Finally, **atrial arrhythmias are rare (especially atrial flutter) and should be considered a sign of cardiac rejection until proven otherwise** with endomyocardial biopsy..

X. Hypertension.

Hypertension is a common problem post-cardiac transplantation. Its pathogenesis is multifactorial, and includes: 1) increased central sympathetic output, 2) the development of insulin resistance/metabolic syndrome, due to steroid therapy and central adiposity, 3) increased release of endothelin-1, 4) decreased renal function secondary to calcineurin inhibitors.

Some considerations should be taken into account in the selection of antihypertensive agents

1. Orthostasis is common; therefore, **α -blockade is poorly tolerated**.
2. Renal dysfunction is common; in particular, calcineurin inhibitors can cause a Type IV renal tubular acidosis. Therefore, ACE inhibitors or angiotensin receptor antagonists often poorly tolerated early, as they may exacerbate hyperkalemia or renal dysfunction.
3. Chronotropic insufficiency is present as a result of cardiac denervation. Therefore, β -blockers may be poorly tolerated. Often, this manifests as a reduction in functional capacity. β -blockers also may exacerbate hypertriglyceridemia.

Therefore, hydralazine and nitrates, as well as amlodipine often are used as anti-hypertensive agents early post-transplant. Later, judicious addition of ACEI/ARB is often better-tolerated. In contrast, α -blockers are almost never tolerated by these patients. β -blockers may be of use in some patients later in their course; however, they often still cause functional limitation that often is under-recognized by the patient and their physicians.

XI. Dyslipidemia

Dyslipidemia is very common post-transplantation, usually manifesting as increased triglycerides and low HDL levels. Of course, LDL levels may also be elevated, especially in those patients who were transplanted for ischemic cardiomyopathy. Typically, lipid levels are relatively low early post-transplant as a result of suppression by the elevated cytokine levels present in advanced heart failure. However, as patients recover from the transplant surgery and develop weight gain and insulin resistance from their steroid therapy, dyslipidemias manifest.

It is important to recognize that there are specific limitations to standard lipid therapies as a result of drug-drug interactions, as well as the specific type of dyslipidemia most common in post-transplant patients:

1. β -blockers may exacerbate hypertriglyceridemia. This is true for atenolol, metoprolol and carvedilol
2. Statin therapy has been shown to be of benefit in post-transplant patients. However, cyclosporine and tacrolimus both inhibit the metabolism of those statins metabolized by cytochrome P450 3A4 (i.e., lovastatin, simvastatin, atorvastatin). Therefore, the maximum-tolerated doses of those statins are approximately 75% lower than the maximum doses for those agents in patients not also receiving cyclosporine or tacrolimus. No adjustment is needed in pravastatin doses.
3. Bile acid sequestrants interfere with the absorption of cyclosporine, which is highly lipophilic. They do not interfere with the absorption of tacrolimus.
4. There is practically no data on the use of ezetimibe in cardiac transplant patients.
5. Fibrates are useful in patients with severe hypertriglyceridemia. Fenofibrate probably is safer than is gemfibrozil, especially in combination with a statin.

XII. Osteoporosis Prophylaxis.

Osteoporosis is common in transplant patients, owing to the use of steroids. Therefore, patients should receive **calcium supplementation**, e.g., OsCal +D, 500 mg bid or Extra-strength Tums 500 mg bid-tid. Other medications should be considered in patients with osteopenia:

- HRT (women):
 - Consider estrogen patch (less TG increase)
- Testosterone (men):
 - Testosterone cypionate/enanthate 100 mg IM q 2-4 weeks
- Calcitonin (Miacalcin®):
 - 1 spray (200 IU) qd (alt. nostril)
 - AE: local nasal irritation
- Alendronate (Fosamax®):
 - 70 mg PO qSat
 - AE: Abdominal pain, diarrhea, constipation, dysphagia, odynophagia, retrosternal pain
- Pamidronate (**as alternative to alendronate in 1st 6 mos post-transplant**):
 - 60 mg in NS 250 mL iv over 90-120 min **X1**

XIII. Other Considerations:

The following should be considered in all patients:

- ASA 81 mg qd to prevent transplant atherosclerosis

- Magnesium oxide 400-800 mg PO daily-tid, due to the Type IV RTA-associated hypomagnesemia
- Ulcer prophylaxis:
 - H2-blocker (NOT cimetidine)
 - PPI if refractory
- Skin Cancer prophylaxis, due to high risk of skin cancer in immunosuppressed patients.

Appendix 1.

Pre-Cardiac Transplant Work-Up University of Washington Medical Center

Note: All work-up labs, consults and diagnostic testing, including right heart cath, should be cc'd or referenced to Mail Box # 356310, UWMC code #90033

Laboratory Studies

- CBC with diff and PLT
- Coagulation screen
- Mini and general panels
- Sedrate and Uric Acid
- Liver function tests
- ANA reflexive panel
- SPEP and UPEP
- antiomyocardial antibody
- Iron studies
- Thyroid studies
- Prostate specific antigen
- Fasting lipid panel
- Hep, A, B and C antibody screens
- HSV antibody screen
- EBV antibody screen
- VZ antibody screen
- HIV antibody screen
- RPR antibody screen
- Rubella and Measles antibody screen
- Toxoplasma IgG and IgM
- 24 hour urine creatinine clearance and protein
- UA
- Blood type
-

Diagnostic Studies

- Right heart catheterization, MUGA and ECHO
- PFT's (spirometry, volumes, MVV, DLCO)
- PA and Lat CXR
- 12-lead ECG
- Skin test with controls (PPD, Mumps, Candida, Trichophyton)
- Stool guiac x 3
- Vascular studies (carotid and LE) if patient is diabetic, hyperlipidemic, has history of vascular problems or CAD
- Pap smear and mammogram

Consults

- Dental evaluation (by either patient's own dentist or at UWMC)
- Social Work evaluation (Lydia Carroll, MSW, Alice Chang, MSW)
- Nutrition evaluation
- Financial counseling (UWMC Financial Services)
- Patient Education (Cardiothoracic Transplant Nurse Coordinators)

Questions regarding the work-up process should be addressed to either the Cardiac Transplant Attending or Cardiothoracic Transplant Nurse Coordinator, contacted through the UWMC Paging Operator at (206) 548-6190 or the Cardiac Transplant Services Office at (206) 685-4884

Appendix 2.

Cardiac Transplant Immunosuppression Card, Side 1

	Steroid	Azathioprine (Imuran®) or MMF (CellCept®)	Tacrolimus (Prograf®)	ATG
Pre-op	Methylpred 500-1000 mg IV X1	4 mg/kg IV <input type="checkbox"/> 1 mg/kg IV if on allopurinol <input type="checkbox"/> 2 mg/kg IV if WBC<4000	NONE	NONE
Intra-op	Methylpred 500-1000 mg IV X1 After CPB	NONE	NONE	Day 0: 1.5 mg/kg when bypass clamp removed
Post-op Days 0-1	Methylpred 125 mg IV q8h X3	MMF 1 gm PO or IV q12 h; hold for WBC<4000	NONE	Day 1: 1 mg/kg at 21:00 (+Tyl 650 mg/Ben 50 mg IV)
Post-op Day 2	Pred 0.15 mg/kg/dose bid	Continued	If Cr<2 and taking PO, 1 mg PO bid	NONE
Post-op Day 3	Continued	May ↑ to 1.5 gm PO bid if tolerated and WBC>4000	If Cr<2, ↑ tacrolimus; goal level is 12-15 ng/mL for Months 0-3	1 mg/kg at 21:00 (+Tyl 650 mg/Ben 50 mg IV)
Post-op Day 4	Continued	Continued	Continued	NONE
Post-op Day 5+	Continued X6 weeks, then taper	Continued	Continued	1 mg/kg at 21:00 (+Tyl 650 mg/Ben 50 mg IV)

***Consider IL-2 blocker (daclizumab 1 mg/kg IV X1 dose if tacrolimus level <8 ng/mL on Day 7 or patient has impaired renal function**

***Goal tacrolimus level for 1st 9 months is 12-15 ng/mL**

Cardiac Transplant Immunosuppression Card, Side 2

Prophylaxis Indication	Timing	Agent/Dose
Surgical Antibiotics	<input type="checkbox"/> until chest tubes removed	<input type="checkbox"/> Cefazolin 1 gm IV q8h* <input type="checkbox"/> If PCN allergic, Vancomycin 1 gm IV q12h*
Candidiasis	<input type="checkbox"/> Day 0+	<input type="checkbox"/> Nystatin 5 mL swish and swallow PO qid OR <input type="checkbox"/> Clotrimazole 10 mg troche PO qid
Pneumocystis	<input type="checkbox"/> Day 14+	<input type="checkbox"/> Single-strength trimethoprim/sulfamethoxazole PO daily
Cytomegalovirus	<input type="checkbox"/> (NONE if BOTH donor/recipient CMV-neg) <input type="checkbox"/> While NPO <input type="checkbox"/> When taking PO	<input type="checkbox"/> Ganciclovir 5 mg/kg IV q12h* <input type="checkbox"/> Ganciclovir 1000 mg PO tid X3mo*
HSV/EBV	<input type="checkbox"/> Month 4-6 (when off ganciclovir) <input type="checkbox"/> Month 6+	<input type="checkbox"/> Acyclovir 400 mg PO tid* <input type="checkbox"/> Acyclovir 200 mg PO tid
Stress Ulcer Prophylaxis	<input type="checkbox"/> While NPO <input type="checkbox"/> When taking PO	<input type="checkbox"/> Ranitidine 50 mg IV q8h* <input type="checkbox"/> Pantoprazole (Protonix®) 40 mg PO daily
Prevention of Graft Atherosclerosis	<input type="checkbox"/> When taking PO	<input type="checkbox"/> ASA 81 mg PO daily <input type="checkbox"/> Pravastatin 20 mg PO qPM
Prevention of Osteoporosis	<input type="checkbox"/> When taking PO	<input type="checkbox"/> Calcium carbonate 1 gm PO bid <input type="checkbox"/> Consider Pamidronate IV or Fosamax (consult pharmacist)
Vitamin Supplement	<input type="checkbox"/> When taking PO	<input type="checkbox"/> Multivitamin with folate

***Consult pharmacist for dosage adjustment in renal insufficiency**