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Research Article

Heart Transplant : Post Discharge Follow Up an a Developing Setup: An Update

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2. Keywords

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1. Introduction

Post heart transplant is a period where the recipient's body and the donor heart are both in a state of adaptation fraught with several hazards. It requires the a comprehensive involvement of the transplant surgeon and team, and the patient for mitigating the post transplant mortality and morbidity as well as increasing the chances of success and quality of the recipients life.

For grasping the core issues which should be focused on the post discharge period, an overview of the primary areas of concerns during the follow up after Heart Transplant is essential.

1. Diagnosis and management of Rejections

2. Tailoring the immunosuppression regimen

3. Infections - Prophylaxis, Diagnosis, Treatment

4. Post Transplant Malignancies: Lympho-proliferative disorders

5. Cardiac Allograft Vasculopathy (**Figure 1**)

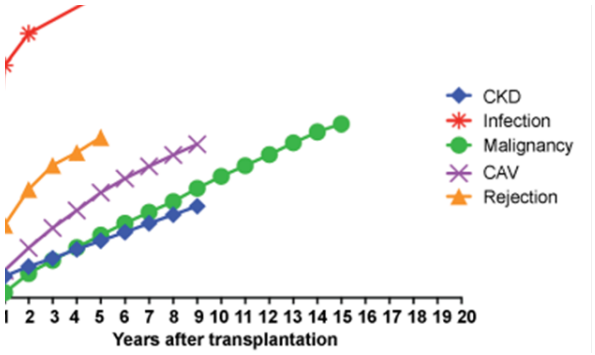

Figure 1: Cumulative incidence of complications during post-heart transplant period based on published data [1]. CKD : Chronic Kidney Disease, CAV: Cardiac Allograft Vasculopathy

1.1. Overview of Complications [2-7]

1.1.1. Causes of Death: There are four major causes of death after cardiac transplantation, which occur at different times [2]

- Sudden (acute) rejection
- Infections other than cytomegalovirus
- Artery disease in the transplanted heart vessels (allograft vasculopathy)
- Lymphoma and other malignancies

1.1.2. Early Mortality: Cardiac transplant recipients have an average of one to three episodes of rejection in the first year after transplantation. Between 50 and 80 percent of people experience at least one rejection episode. Acute rejection is most likely to occur in the first three to six months, with the incidence declining significantly after this time [2,3].

In the first year, most deaths are due either to acute rejection (18 percent) or infections (22 percent). Infections often develop as a result of the anti-rejection medications and weakened immune

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system that are required to prevent rejection.

1.1.3. Late Mortality: Rejection is less common after the first year, and by four to five years after transplantation, less than 10 percent of deaths are the result of rejection [2,3].

However, development of rapidly progressing coronary artery disease in the arteries of the transplanted heart (called allograft vasculopathy), becomes one of the most common causes of death by five years. The number of fatal cancers increases over time as well [4].

Infections remain a significant cause of death after the first year. These infections are the result of a weakened immune system, and can develop from common bacteria and viruses in the community or from uncommon infections [4].

Post-transplant Lymphoproliferative Disease (PTLD) is a type of cancer that occurs in patients who use immunosuppressive medications. PTLD includes non-Hodgkin lymphoma. Most cases of PTLD occur in the first year after transplant. Among patients who develop lymphoma, the overall survival rates are between 25 to 35 percent at five years (**Table 1** and **2**).

Table 1: Follow up schedule [4].

Test	1 month	1 month – 6 month	6 months to 1 year	Annualy
Heart Biopsy	Weekly until 1 month	2nd weekly next 5 months	6th, 8th, 1 year	After 1 year, only if indicated
Renal Function and Immunosuppressive levels	As above	As above	As above	As above
Chest Xray, ECHO				At year 1
Coronary Artery disease screening				Yearly

Table 2: Post Transplant schedule for Endomyocardial biopsy [4].

Biopsy 1, 2, 3, 4, and 5:	Weekly
Biopsy 6, 7, and 8:	Every 14 days
Biopsy 9 and 10:	Every 3 weeks
Biopsy 11, 12, and 13:	Every 4 weeks
Subsequent biopsies during the 1st year after HT:	Every 5 to 6 weeks

3. Immunosuppresion

Maintenance immunosuppression after HT usually consists of:

1) Corticosteroid

2) A (Cycloneurin Inhibitor) CNI (Cyclosporin A or Tacrolimus

3) An antimetabolite (azathioprine [AZA] or mycophenolate mofetil [MMF]).

The m-TOR inhibitors, everolimus (EVL) and sirolimus (SRL), may also be used in clinical practice. The mode of action of the drugs is mentioned in (**Table 3** and **4**).

Table 3: Mechanisms of action and major side effects of maintenance immunosuppressive drugs in Heart Transplantation.

Mechanisms of action and major side effects of maintenance immunosuppressive drugs in heart transplantation.

Drug	Mechanism of action	Effects	Major side effects (excluding infection and malignancy)
Calcineurin inhibitors			
Tacrolimus	Inhibition of the enzyme calcineurin	Prevention of proliferation and differentiation of T-cells	Drug-drug interactions, nephrotoxicity, neurotoxicity, hypertension, dyslipidemia, diabetes
Cyclosporine	Inhibition of the enzyme calcineurin	Prevention of proliferation and differentiation of T-cells	Drug-drug interactions, nephrotoxicity, neurotoxicity, hypertension, dyslipidemia, gingival hyperplasia, hirsituism
Antimetabolites			
Mycophenolate mofetil	Inhibition of the cell cycle	Prevention of proliferation and differentiation of T-and B-cells	Leukopenia, gastrointestinal problems
Azathioprine	Inhibition of the cell cycle	Prevention of proliferation and differentiation of T-and B-cells	Pancytopenia, hepatitis, pancreatitis
Mammalian target of rapamycin inhibitors			
Everolimus	Inhibition of the enzyme mammalian target of rapamycin	Prevention of proliferation and differentiation of T-and B-cells	Drug-drug interactions, dyslipidemia, pancytopenia, delayed wound healing, oral ulcers, pericardial and pleural effusions
Sirolimus	Inhibition of the enzyme mammalian target of rapamycin	Prevention of proliferation and differentiation of T-and B-cells	Drug-drug interactions, dyslipidemia, pancytopenia, delayed wound healing, oral ulcers, pericardial and pleural effusions

Table 4: The mode of action of the drugs.

Class / Drug	Dosing
Calcineurin Inhibitors	
Cyclosporine	Based on goal trough levels; usual requirement 4-15 mg/kg/day divided twice daily
Tacrolimus	Based on goal trough levels; usual requirement 0.05- 0.3 mg/kg/day divided twice daily
Anti-proliferatives	
Azathioprine	Based on white blood cell counts; usual requirement 1 to 3 mg/kg/day
Mycophenolate Mofetil	25–50 mg/kg/day or 1,200 mg/m^2/day divided twice daily; may target MPA trough levels 1.5-2
m-TOR Inhibitors	
Sirolimus	Based on goal trough levels; usual requirement 1–3 mg/m^2/day
Everolimus	Based on goal trough levels; usual requirement is 0.8mg/m^2/day
Corticosteroids	
Prednisone	Significant institutional variation; typical maintenance dose 0.05- 0.3 mg/kg/day

4. Rejection

The recipient's body may reject a donor organ through hyperacute rejection, acute cellular rejection, or antibody-mediated rejection. The risk for developing rejection is the highest in the first six months following heart transplantation, with a decrease as the time from transplantation increases Sex and age are both linked to rejection risk, with females and younger individuals being at higher risk.

4.1. Hyperacute Rejection

During the immediate post-transplant phase, after cross clamp removal, hyperacute rejection may occur when the recipient has pre-existing donor directed human leukocyte antigen (HLA) antibodies [7]. Hyperacute rejection is now uncommon as a result of both antibody screening prior to transplantation (panel reactive antibodies (PRA)), and blood type matching [3,7].

4.2. Acute Cellular Rejection

This remains a frequent complication post-transplant. It involves recipient T-cells recognizing donor HLA molecules by means of antigen-presenting cells. Around 20 to 40% of patients will experience acute cellular rejection between 6 and 12 months post-transplant, though most patients are asymptomatic without allograft dysfunction.

4.3. Acute Rejection

The clinical presentation of acute rejection varies widely. Patients may be asymptomatic or may have nonspecific clinical signs and symptoms, including fever, anorexia, leukocytosis, and mild hypotension. In rare cases, acute rejection manifests with severe hypotension and circulatory collapse.

4.3.1. Pathology: The primary process leading to acute rejection is acute cellular rejection, which is T cell mediated. Donor antigen presenting cells (APCs) may be directly recognized by recipient T cells, or donor antigens may cross into the recipient to be taken up by recipient APCs. The presentation of antigens to T cells via APCs causes conformational changes in the T cell receptor. In the presence of a costimulatory molecule, i.e., B7 (CD80 or CD86), on the APC interacting with CD28 on the T cell, promotion of T cell proliferation and cytokine production occurs. Following the sensitization of effector cells, there is a migration of lymphocytes into the allograft with subsequent activation of either the FAS-FAS ligand or perforin/granulolysin pathway resulting in myocyte death [2,3,7].

4.3.2. Diagnosis: Because these clinical signs and symptoms lack a high degree of sensitivity or specificity in the diagnosis of acute rejection, the gold standard diagnostic test is a tissue biopsy.

Percutaneous endomyocardial biopsy is performed as a part of routine surveillance protocols after heart transplantation. A bioptome is passed through a sheath in the right internal jugular vein and advanced through the tricuspid valve into the right ventricle, where tissue biopsies are taken [9].

Due to patchy involvement, 4-6 biopsies are taken. Possible frequent complication is Tricuspid Regurgitation as shown in (**Figure 2**) [9].

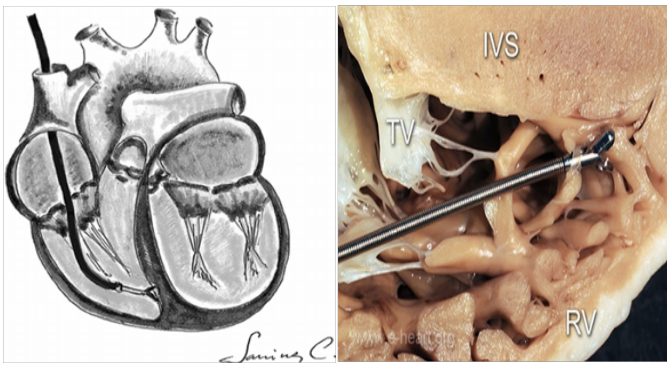

Figure 2: Tricuspid Regurgitation.

4.3.4. Alternative Noninvasive Techniques to Monitor Cardiac Allograft Rejection [11,16]

Emerging and promising techniques include magnetic resonance imaging, wall motion analysis with tissue Doppler imaging, electrical event monitoring with ventricular evoked response amplitude assessment, identification of peripheral blood markers of rejection (e.g., P-selectin, prothrombin fragments, B-type natriuretic peptides, troponin), imaging for necrosis with antimyosin antibody–based scintigraphy,and imaging for apoptosis with technetium 99m–labeled annexin V. Cardiac biopsy grading as mentioned in (**Table 5**).

Table 5: ISHLT : Standardised cardiac biopsy grading of ACR.

Grade	Criteria
Grade 0R†	No rejection
Grade 1R, mild	Interstitial and/or perivascular infiltrate with up to one focus of myocyte damage
Grade 2R, moderate	Two or more foci of infiltrate with associated myocyte damage
Grade 3R, severe	Diffuse infiltrate with multifocal myocyte damage ± edema ± hemorrhage ± vasculitis

4.3.5. Treatment [17] (Augmentation of immunosuppression): Asymptomatic patients with low grade rejection detected on surveillance biopsy may be managed with adjustments in the patient's regimen, titration to drug levels, and follow-up biopsy.

Patients with moderate to severe acute cellular rejection should be treated aggressively even in the absence of symptoms or graft dysfunction.

In the symptomatic patient, prompt institution of therapy is critical in dependent of the grade of rejection. Options for acute therapy include corticosteroids or ATG as shown in algorithm in (**Figure 3**) and (**Table 6**)

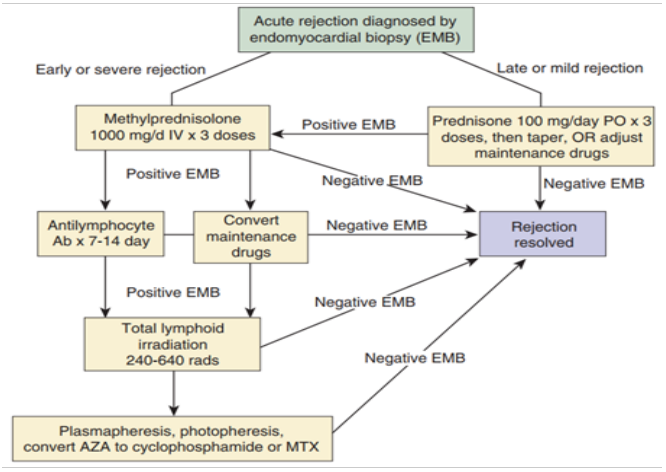

Figure 3: Options for acute therapy.

Table 6

The ISHLT guidelines on the general treatment of ACR.

ACR grade (2004-ISHLT-WF)	Recommended treatment
Asymptomatic ACR grade 1R	Usually no treatment required
Asymptomatic ACR grade 2R	High-dose oral CSs for three to five days–or – High-dose intravenous CSs for three days
Asymptomatic ACR grade 3R	High-dose intravenous CSs for three days–and – Addition of ATG in case of evidence of graft dysfunction or absence of histologic resolution
Symptomatic ACR (grade 1R-3R)	High-dose intravenous CSs for three days–and – Addition of ATG in case of HC or no improvement after 12-24h

ISHLT (International Society for Heart and Lung Transplantation), ACR (Acute cellular rejection), WF (Working formulation), CSs (Corticosteroids), ATG (antithymocyte globulin), HC (hemodynamic compromise). Abbreviated version of original guidelines [6].

4.4. Antibody-Mediated Rejection[17]

This type of rejection is characterized by an antibody-driven immune response to vascular endothelial antigens in the allograft, involving both B-cells and T-cells. Though not as common as acute cellular rejection, antibody-mediated rejection has an estimated incidence of 10 to 20% in the first year post-transplant. Mixed rejection -simultaneous acute cellular rejection and antibody mediated rejection-can be seen in as many as 25% of acute rejection cases [4].

The principles of management for both ACR and AMR are same: aggressive hemodynamic management along with augmentation of the immunosuppressive regimen to maximize the effort against circulating DSAs and lessen B cell activity. Plasmapheresis, steroid therapy, rituximab, ATG, bortezomib, and IVIG are used in a variety of combinations, as shown in (**Table 7**) (**Figure 4**).

The following algorithm shows the systemic approach of management of graft rejection as in (**Figure 5**) (**Table 8**)

Table 7: Standardized Cardiac Biopsy Grading.

TABLE 98-4 **ISHLT Standardized Cardiac Biopsy Grading: Acute Antibody-Mediated Rejection (AMR)**

Grade	Definition	Substrates
pAMR 0	Negative for pathologic AMR	Histologic and immunopathologic studies are both negative.
pAMR 1 (H+)	Histopathologic AMR alone	Histologic findings are present and immunopathologic findings are negative.
pAMR 1 (I+)	Immunopathologic AMR alone	Histologic findings are negative and immunopathologic findings are positive (CD68+ and/or C4d+).
pAMR 2	Pathologic AMR	Histologic and immunopathologic findings are both present.
pAMR 3	Severe pathologic AMR	Interstitial hemorrhage, capillary fragmentation, mixed inflammatory infiltrates, endothelial cell pyknosis, and/or karyorrhexis, and marked edema and immunopathologic findings are present. These cases may be associated with profound hemodynamic dysfunction and poor clinical outcomes.

From Berry GJ, Burke MM, Andersen C, et al: The 2013 International Society for Heart and Lung Transplantation working formulation for the standardization of nomenclature in the pathologic diagnosis of antibody-mediated rejection in heart transplantation. J Heart Lung Transplant 32(12):1147–1162, 2013.2007.)

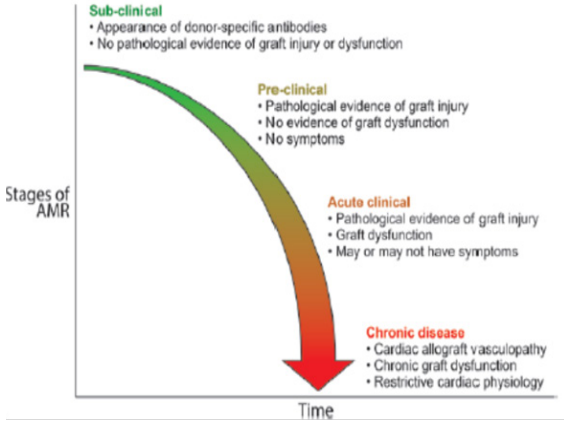

Figure 4: Clinical continuum of AMR [18].

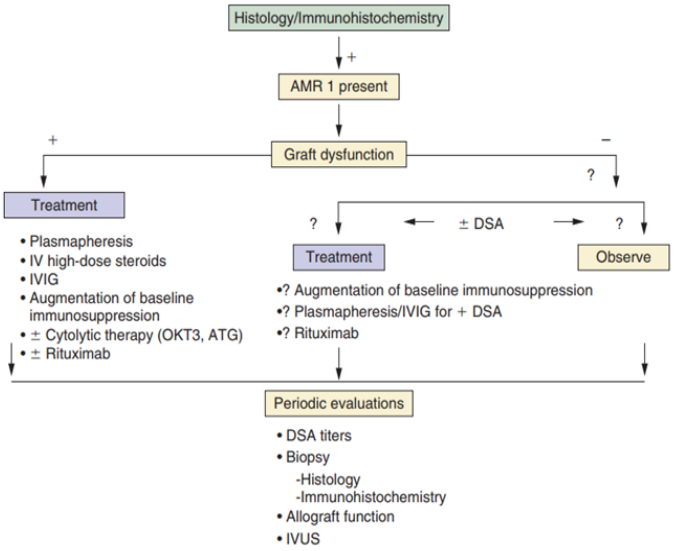

Figure 5: Algorithm for treatment of antibody-mediated rejection (AMR) in cardiac transplant recipients. *ATG,* Antithymocyte globulin; *DSA,* donor-specific antibody; *IV,* intravenous; *IVIG,* intravenous as shown in Table 7 immunoglobulin; *IVUS,* intravascular ultrasound [18]

Table 8: Therapies for antibody mediated rejection.

Table 12 Examples of Therapies for Antibody-Mediated Rejection

Therapeutic modality	Dose	Frequency	Duration
Plasmapheresis	1–2 plasma exchanges	Daily	3–5 days
		Every other day	1–2 weeks
		3 times per week	1–4 weeks
		Once weekly	2–4 weeks
IV Ig	100–1,000 mg/kg	1–3 times per week, often given after each plasmapheresis	1–4 weeks
Rituximab	375 mg/m^2	Once weekly	1–4 weeks

IV Ig, Intravenous immunoglobulin.
Based on Grauhan O et al,[221] Leech SH et al,[226] Michaels PJ et al,[228] Miller LW et al,[229] Kaczmarek I et al,[222] Takemoto SK et al,[85] and Bierl C et al.[396]

5. Infection

An inherent complication of immunosuppression is increased risk for infection. In the first three years after transplantation, infection is the cause of death in 12% to 29% of patients [2]. The pathogens involved vary depending on the time after transplantation.

Early infections in the first month after transplantation are commonly caused by bacteria and often manifest as pneumonia or urinary tract infections. Typical pathogens include Pseudomo-

nas aeruginosa, Escherichia coli, and Staphylococcus aureus. However, the risk of infection decreases over time as immunosuppressive therapy is generally tapered. The proportion of mortality attributable to infection is only 11% to 12% greater than 3 years out from heart transplantation.

5.1. Cytomegalovirus [19-24]

Cytomegalovirus (CMV) is the most common and clinically significant viral pathogen in heart transplant recipients. It may cause a variety of syndromes and has been implicated as a trigger for accelerated CAV. Heart transplant recipients are at high risk for CMV infection because cell-mediated immunity, which is necessary to combat CMV, is impaired by conventional immunosuppressive drugs. CMV infection may manifest either as primary infection or as reactivation of a latent infection. Primary CMV infection may develop in seronegative recipients receiving a heart from a CMV seropositive donor. In such cases, donor leukocytes or the allograft itself may harbour CMV and transmit it to the recipient. The risk of CMV infection is shown in (**Table 9**) and its management approach in (**Table 10**).

Table 9: The risk of CMV infection.

TABLE 98-5 Risk of Cytomegalovirus (CMV) Disease in Populations of Cardiac Transplant Recipients

Donor CMV Serotype Status	Recipient CMV Serotype Status	Antilymphocyte Antibody Therapy	Incidence of Disease (%)
Positive	Negative	–	50-75
Positive or negative	Positive	No	10-15
Positive or negative	Positive	Induction	≈25
		Antirejection	50-75
Negative	Negative	–	≈0*

Table 10: Prevention of CMV infections in heart transplant recipients.

Table 2 Typical Recommendations for the Prevention of Cytomegalovirus in Heart Transplant Recipients

Group	Recommendations/Options
D+/R–	Oral ganciclovir (1000 g PO TID) or valganciclovir (900 mg PO/day) for 3 months *or* IV ganciclovir (5–10 mg/kg/day) for 1–3 months Preemptive therapy generally not preferred due to high risk of disease Some HT centers will add CMV immune globulin for high risk patients
R+	Oral ganciclovir (1000 g PO TID) or valganciclovir (900 mg PO/day) for 3 months *or* IV ganciclovir (5–10 mg/kg/day) for 1–3 months *or* Preemptive therapy. Monitor with nucleic acid testing or CMV antigenemia assay Therapy with IV ganciclovir or oral valganciclovir

CMV, cytomegalovirus; D, donor; HT, heart transplant; IV, intravenous; PO, oral (per os); R, recipient; TID, 3 times daily.

In donor negative/recipient negative transplants, CMV disease is uncommonly seen under two circumstances: transfusion of viable leukocyte containing blood products from a seropositive donor or acquisition of virus in the community through intimate person-to-person contact.

CMV infection can manifest as a mononucleosis-like syndrome, or it may be tissue invasive. The most common sites for tissue invasion are the lung, liver, and gastrointestinal tract. Less common sites include the retina and skin.

Diagnosis made by measurement of viral load with either quantitative polymerase chain reaction or anti genesis assays; by direct culture of the virus from blood, urine, or tissue specimens; or by observation of characteristic histologic changes (enlarged cells containing nuclear inclusion bodies) [23,24].

5.2. Treatment

A combination of intravenous ganciclovir and hyperimmune globulin is used to treat CMV infection [23]. Several populations of cardiac transplant patients benefit from prophylactic treatment against CMV infection. Serologically mismatched patients (seronegative recipient of heart from seropositive donor) are treated with a combination of ganciclovir and hyperimmune globulin for weeks to months after transplantation [23,24]. Often, seropositive recipients are also treated with a course of ganciclovir to prevent reactivation infection. Prophylactic administration of intravenous ganciclovir when antilymphocyte antibody therapy is used to treat rejection reduces the risk for CMV disease to baseline levels.

5.2.1. High Risk of CMV Replication: CMV mismatch (donor positive, recipient negative), Cytolytic induction with ATG, use of MMF in maintainance immunosuppression:

- Antiviral prophylaxis: Valganciclovir per oral 900 mg OD or BD for upto 6 months after transplant (dose adjusted as per kidney function).
- Surveillance of CMV replication - once a week to twice a month for 6 months post transplant: CMV early antigen pp65 in PMNC or CMV DNA by PCR.
- Replace MMF with Everolimus

5.2.2. Low risk of CMV replication

- In centres where regular monitoring of CMV replication not possible-prophylaxis of Herpes virus with Acyclovir 800 mg thrice daily per oral.
- In centres with access to regular diagnosis of CMV replication, if CMV replication is detected, pre-emptive therapy with Valganciclovir.

5.2.3. CMV Disease

- Clinical manifestation after 2-4 weeks.
- Bone marrow suppression, gastroenteritis, fever, impaired kidney function.
- Treatment-IV Ganciclovir 5mg/kg/day BD. Dose adjusted as per kidney function. Effect of therapy monitored by surveillance of CMV replication.

5.3. Herpes Simplex

- Early after transplantation-mucocutaneous herpes simplex – painful aphtous disease in the mouth, lips, tongue.
- If only local apthous ulcer – local application of Acyclovir ointment.
- If difficulty in swallowing – iv Acyclovir followed by oral application.

5.4. EBV

If EBV positive donor and EBV negative recipient – withhold ATG to prevent EBV disease and PLD.

5.4.1. Protozoal: Protozoal pathogens that can appear after heart transplantation include Pneumocystis carinii and Toxoplasma gondii. Pulmonary infection with P. Carinii can be prevented by routine postoperative prophylaxis with trimethoprim sulfamethoxazole or aerosolized pentamidine (for sulfa-allergic patients). Toxoplasmosis may occur in serologically mismatched patients (e.g., T. gondii–seronegative recipient of heart from T. gondii–seropositive donor) but may be prevented by prophylaxiswith atovaquone.

5.4.2. Pneumocystis Jirovecii: Interstitial pneumonia with severe hypoxemia. Diagnosis by special staining or PCR of bronchoalveolar lavage specimen.

- Toxoplasma gondii: high risk when donor is toxoplasma antibody positive and recipient is negative. Diagnosis by PCR or detection of IgM antibodies (difficult due to immunosuppression).
- Antiprotozoal prophylaxis: TMP/SMZ 960 mg tab twice a week upto 6 months post transplant.
- Treatment as in immune compromised status

5.4.3. Fungal Infections: Invasive fungal infections are uncommon after cardiac transplantation, but when they occur, they cause significant morbidity and mortality. Fungal pathogens include Candida albicans and Aspergillus. Treatment consists of fluconazole, itraconazole, or amphotericin B. The prevalent infections in relation to the time frame is enlisted in (**Table 11**)

Table 11: Prevalent infections based on post-transplant time.

Infection Type	Early Infections (< 1 month)	Intermediate Infections (1-6 months)	Late Infections (> 6 months)
Viral	Herpes simplex virus	Human herpesvirus type 6	Herpes simplex virus
		Cytomegalovirus	Cytomegalovirus
		Hepatitis C Virus	Hepatitis C virus
		Hepatitis B virus	Hepatitis B virus
		Varicella Zoster Virus	Varicella Zoster virus
		Human herpes virus type 8	
		Epstein-Barr virus	
		Adenovirus	
		Influenza virus	
Bacterial	Nocardia	Nocardia	Nocardia
	Clostridium difficile	Clostridium difficile	Listeria monocytogenes
	Psuedomonas	Listeria monocytogenes	Mycobacterium tuberculosis
	Vancomycin-resistant enterococci	Mycobacterium tuberculosis	
	Methicillin-resistant Staphlococcus aureus		
Fungal	Candida	Candida	Aspergillus
	Aspergillus	Aspergillus	Pneumocystis carinii
		Pneumocystis carinii	Cryptococcus
		Cryptococcus	
Parasitic		Toxoplasma gondii	Toxoplasma gondii
			Trypanosoma cruzi
Other	Pneumonia		Community acquired infections
	Wound/Line infection		
	Urinary tract infection		

5.5. Malignancies

Another life-threatening consequence of long-term IS following transplantation is cancer. IS drug regimens predispose individuals to malignancy through several mechanisms, including impaired immune responses against malignant cells and oncogenic viruses [24]. The incidence of malignancy increases with time following transplant, with 2.6%, 14.1%, and 27.9% of individuals developing any malignancy after 1, 5, and 10 years respectively [25]. This incidence is approximately 3 to 4 fold greater than age-matched controls in the general population.

Skin malignancies and lymphomas are the most commonly reported cancers, with skin malignancies affecting 19.8% of patients, and lymphomas 1.8% of patients 10 years following heart transplant. The most prevalent skin malignancies following transplant include basal cell and squamous cell carcinomas. In comparison, lymphomas are generally due to post-transplant lymphoproliferative disorder. Early post-transplant lymphoproliferative disorder (within 1 year of transplant), is most commonly caused by infection with Epstein-Barr virus and typically affects B-cells. Late post-transplant lymphoproliferative disorder (> 1 year following transplant) is more likely to be Epstein-Barr virus negative and non-B cell. Other reported cancers following heart transplant include Kaposi's sarcoma, adenocarcinoma, melanoma, as well as solid tumors affecting the prostate, lung, bladder, breast, cervix, colon, and kidney [24-28].

Risk factors for malignancy following heart transplant can be divided into general and cancer-specific categories. Generally, cancer risk following transplant is dependent on the duration and

intensity of IS, as well as age 24-28.

In comparison, risk factors for post-transplant lymphoproliferative disorder include Epstein-Barr virus infection, high intensity of IS, and antibody induction therapy using OKT3 [24-28].

Malignancy is one of the most common causes of death 3-5 years following transplant. In fact, up to 24% of deaths after 5 years following transplant are directly caused by malignancy. This is especially true of individuals who develop lymphomas as compared to skin malignancies.

Patients who develop malignancy may require a reduction in their IS doses, which can lead to acute rejection .Such reduction is often performed in the case of post-transplant lymphoproliferative disorder, as minimizing IS has been shown to improve overall survival. However, this survival benefit is at the expense of a 10% increased risk of sudden cardiac death due to acute rejection, highlighting the challenge in balancing IS versus cancer risk [2].

Current guidelines suggest that IS should not be reduced in patients with solid tumors that are unrelated due to the lymphoid system, due to a lack of sufficient evidence to support the benefit [2]. Either way, reductions in IS doses should be closely monitored and individualized in an attempt to balance malignancy versus allograft rejection [2]

Specific IS drugs may prevent the recurrence of malignancy. Proliferation signal inhibitors, such as sirolimus, have been shown to have anti-neoplastic properties in addition to their IS actions .This contrasts with the commonly used CNIs, which have been shown to promote malignancy independently of their IS functions [2].

5.6. Screening

To prevent malignancy, all heart transplant recipients should receive age appropriate screening for breast, colon, and prostate cancer, as well as increased skin cancer screening with yearly dermatologic exams [17]. Furthermore, high-risk patients should be evaluated closely for the development of post-transplant lymphoproliferative disorder through regular screening of Epstein-Barr virus load [17]. For those at particularly high risk of malignancy, reduction in chronic IS should be done if possible. If cancer does occur, IS doses should be altered as appropriate, and patients should receive treatments specific to their cancer, such as chemotherapy or anti-B cell monoclonal antibodies in the case of post-transplant lymphoproliferative disorder. With regular screening and balanced, individualized interventions, it may be possible to reduce this common complication [17].

6. Cardiac Allograft Vasculopathy

The development of cardiac allograft vasculopathy remains the Achilles heel of cardiac transplantation. Development of cardiac allograft vasculopathy represents the major determinant of long-term survival in patients after heart transplantation. Due to graft denervation, these patients seldom present with classic symptoms of angina pectoris, and the first clinical presentations are progressive heart failure or sudden cardiac death. The treatment of the established vasculopathy is disappointing, so the primary effort should be directed toward early prevention and diagnosis. Due to diffuse vascular changes, revascularization procedures are restricted only to a relatively small proportion of patients with favourable coronary anatomy. Severe vasculopathy has a poor prognosis and the only definitive treatment is retransplantation.

6.1.Aetiopathogenesis [29]

The pathophysiologic features of CAV, although not completely understood, likely involve components of both immune-mediated and non-immune-mediated endothelial damage, and passenger “native vessel” atherosclerosis [10] histocompatibility mismatch, acute rejection episodes and chronic inflammation.

The activation of CD4+ and CD8+ T cells leads to further synthesis of cytokines, which perpetuate the ongoing cascade of events that lead to CAV. The most important cytokines in allograft rejection are interleukin-2 (IL-2), interferon-gamma (IFN-γ) and tumour necrosis factor-alpha (TNF-α). IL-2 induces T-cell proliferation and differentiation, IFN-γ activates macrophages, and TNF-α itself is cytotoxic to the transplanted heart. In addition, TNF-α acts to increase MHC class I expression, while IFN-γ increases the expression of both MHC classes I and II molecules. Overall, these cytokines can lead to chronic graft rejection. IFN-γ and TNF-α also induce the leukocyte vascular cell adhesion molecule-1, which promotes monocyte adhesion and entry through the endothelium, leading to CAV.

6.2. Nonimmunologic Factors

Hyperlipidemia and insulin resistance are the most significant nonimmunologic factors, occurring in 50%–80% of the heart transplant population as shown in (**Figure 6**).

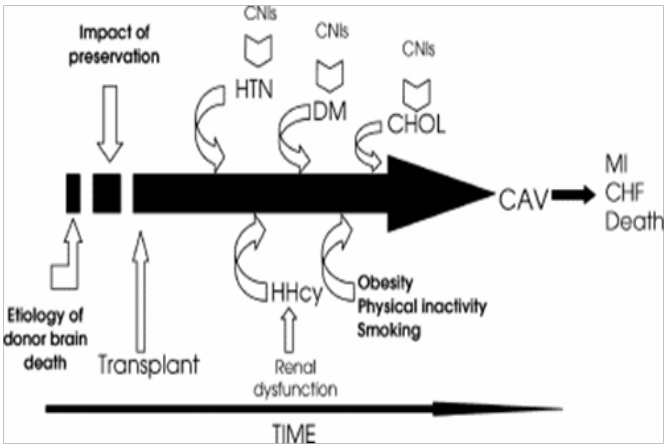

Figure 6: Pathophysiology of cardiac allograft vasculopathy.

Pathophysiology of cardiac allograft vasculopathy (CAV) [29]
CHF= Congestive Heart Failure
CHOL = Cholesterol
CNI = Calcineurin Inhibitors
DM = Diabetes Mellitus
HHcy = Hyperhomocysteinemia
HTN = Hypertension
MI = Myocardial Infarction

- Cause of donor brain death
- Cytomegalovirus (CMV) infection
- Age, sex, obesity
- Dyslipidemia, hyperhomocysteinemia (HHcy)
- Diabetes mellitus, hypertension, smoking
- Ischemia–reperfusion injury

The endothelial damage involved in CAV can be categorized into either denuding or nondenuding injury. In nondenuding injury a rapid replacement of injured endothelial cells leads to endothelial dysfunction. Both immune-related and nonimmune-related factors contribute to nondenuding injury.

In contrast, denuding injury is caused by ischemia–reperfusion injury during transplantation or during episodes of acute cellular rejection. This results in the loss of large stretches of endothelium along the vessel, which causes significant endothelial dysfunction.

Denuding injury allows for blood components and circulating cytokines to have direct contact with the subintimal layers. This can lead to significant proliferation of smooth-muscle cells. Therefore, CAV can be initiated or exacerbated by several processes that can lead to denuding or nondenuding injury. These include ischemia–reperfusion injury, immune activation, viral infection and injury from immunosuppressive drugs.

Hyperlipidemia is commonly seen in cardiac transplant patients for several reasons. Many of these patients are hyperlipidemic before transplantation. In addition, the immunosuppressive therapy given to patients, especially calcineurin inhibitors, may result in or exacerbate pre-existing dyslipidemia. Hypercholesterolemia promotes fibrofatty proliferative changes to the intimal hyperplasia seen in most patients with CAV [15].

In solid-organ transplant recipients, HHcy is extremely common and occurs early with a rate as high as 80%–90%. HHcy can damage cells by several mechanisms, but primarily by affecting the endothelium. HHcy results in reduced endothelial nitric oxide production, impaired arterial response to vasodilators and increased expression of procoagulant factors. The neutrophil–endothelium interaction is promoted in the setting of HHcy, allowing for the presence of more neutrophils in the intima. All of these alterations in the endothelial wall are caused by alterations in the redox state induced by high homocysteine levels.

Hypertension, smoking, diabetes mellitus and other risk factors for atherosclerosis are associated with CAV. Hypertension in transplant patients can be present preoperatively or postoperatively secondary to immunosuppressive medication, such as cyclosporine. Hypertension causes endothelial injury by promoting the formation of intimal hyperplasia, which eventually gives rise to atherosclerotic lesions.

6.3. Diagnosis

Cardiac denervation at the time of heart transplantation usually prevents transplant patients from experiencing angina, which is an important warning sign for heart disease. Only 10%–30% of heart transplant recipients regain any innervation to the heart. Because of this lack of early clinical symptoms, transplant patients with CAV typically present late with silent myocardial infarction, loss of allograft function or sudden death [31].

Another difficulty faced by clinicians in diagnosing CAV is coronary remodelling and the diffuse nature of the disease. Angiography measures luminal diameter and compares the narrowing at plaques to normal reference diameters and previous angiograms in order to understand the severity and rate of disease progression. CAV, however, shows no initial decrease in luminal diameter due to vascular remodelling. Only when the process is more advanced does the lumen narrow and angiographic detection become possible. Since CAV involves the entire coronary arterial tree, angiography may convey the impression of less-than-actual vessel narrowing at plaque sites. Thus, angiography, although it is a good screening tool for CAD, often underestimates CAV, and in some patients with evenly distributed disease throughout the coronary tree, CAV can be missed altogether [29].

Despite the poor sensitivity of angiography, it is still widely used as a screening test for vascular disease. Johnson and associates developed a classification system 32 based on the varying morphologies in CAV to aid in its diagnosis using angiography. Briefly, type A lesions appear as discrete proximal tubular stenoses, type B as diffuse concentric middle or distal stenoses, with type B1 having an abrupt narrowing and type B2 having a smooth concentric tapering. Finally a type C angiographic appearance indicates irregular vessels with distal lesions and loss of small branches. Diagnosis of CAV requires type B or C lesions and comparison with previous and recent angiograms to note disease progression.

A more sensitive tool is intravascular ultrasonography (IVUS). IVUS is useful for detecting the extent of intimal thickening by imaging vessel wall structure rather than simply luminal diameter. IVUS has an axial resolution of 50–80μm. Unfortunately, it is physically restricted to the larger epicardial arteries, and thus cannot be used to screen for CAV throughout the entire heart.

One year after transplantation, IVUS detects CAV in 50% of patients whereas angiography detects disease in only 10%–20% of patients [33].

With IVUS, normal coronary intimal thickness ranges between 0.10 and 0.30 mm. Hence, CAV is considered present when intimal thickness exceeds 0.3mm or when the sum of the intimal and medial thickness exceeds 0.5 mm. At greater than 0.6-mm intimal thickening, patients are 10 times more likely to experience a cardiac event [33] (**Figure 7**).

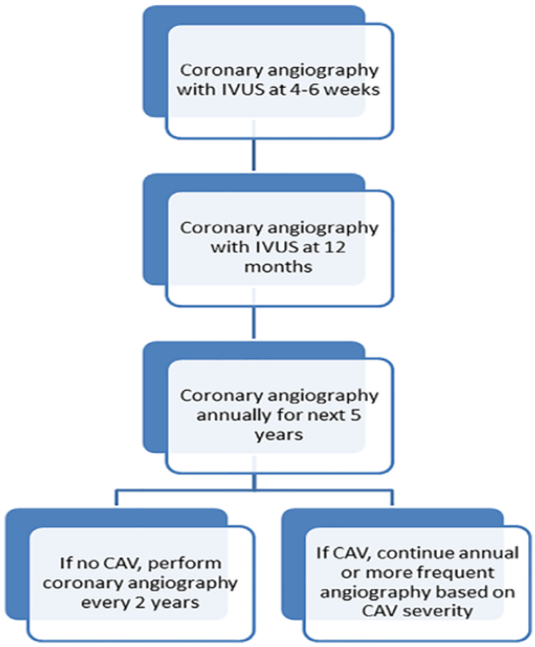

Figure 7: CAV surveillance
Flowchart outlining the current standard of care in cardiac allograft vasculopathy surveillance [34].

6.4. Treatment [31-34]

6.4.1. Prevention & Risk Reduction, Early Diagnosis, Treatment and Disease Reversal

A)Pharmacotherapy

- **Statins**: Statins are a mainstay in pharmacotherapy for OHT patients given their cholesterol-independent immunomodulating effects. They are typically instituted by the end of the first week or during the second week after heart transplantation. Pravastatin is started with 20 mg/d and then increased to 40 mg/d if tolerated . Simvasta-tin is started with 5 mg/d and increased to 10 and 20 mg/d . The early initiation of statins is of utmost importance, as their later introduction in transplant patients did not have a favourable effect on graft prognosis although it reduced serum cholesterol level . The favourable effects of statins, besides lowering plasma lipids, may be explained with anti-inflammatory activity, cytokine suppression, and improvement of endothelial function [29].

- **ACE Inhibitors and ARB :** Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) reduce the incidence of CAV by several mechanisms including a decrease of peripheral mononuclear cells that differentiate into smooth muscle-like cells, thereby theoretically altering a cascade of events critical to CAV advancement.Increased levels of angiotensin II (AII) receptor messenger RNA (mRNA) may be involved in the pathogenesis of CAV via promotion of inflammation, extracellular matrix remodeling, apoptosis, and fibrosis.

- **Antioxidant :** Vitamin C (2 x 500mg/day, Vit E (2 x 400IU/day)

- **Calcium Channel Blocker**

- **Aspirin**

B) Immunosupression

Immunosuppressive agents can decrease the risk of acute allograft rejection and smooth muscle cell proliferation and therefore may reduce the frequency and severity of CAV. In recent years, there has been animportant transition to preferential use of TAC over cyclosporin and mycophenolate mofetil over azathioprine. When comparing immunosuppression with TAC as opposed to cyclosporin, studies have demonstrated greater prevention of acute allograft rejection with a TAC-based immunosuppression protocol [33,35].

- Proliferating Signal Inhibitor

Sirolimus/ Everolimus: The ISHLT guidelines recommend everolimus, sirolimus, or mycophenylate in the post-OHT period to minimize the onset and advancement of CAV [4].

C) PCI : Given the diffuse nature of CAV as well as involvement of the distal microvasculature, PCI is considered palliative despite high initial success rates (91%–100%)

D) Surgical Revascularisation : Dissappointing results due to diffuse and distal vessel involvement.

E) Re-Transplant: CAV is a multifactorial disease that remains the major limitation to long-term survival after heart transplantation. Methods of diagnosis have improved significantly with the use of IVUS in addition to angiography. Since treatment of CAV is limited and usually involves repeat transplantation, prevention of immunologic and nonimmunologic risk factors is of critical importance. CAV is conceptually very similar to post-transplant disorders in other organs (e.g., bronchiolitis obliterans with organizing pneumonia, biliary cirrhosis).

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