INSHLT guidelines for Surgical treatment of End Stage heart failure, heart and lung transplantation.

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1. PREAMBLE:

End-stage heart and lung diseases have become a major problem in India. As per WHO's Global Status Report on NCDs -2014, non-communicable diseases (NCDs) contribute to around 5.87 million deaths that account for 60 % of all deaths in India. Cardiovascular diseases (coronary heart disease, stroke, and hypertension) contribute to 45% of all NCD deaths followed by chronic respiratory disease (22 %). The actual incidence of heart failure is not known. As per Huffman and Prabhakaran [1], the prevalence of heart failure in 2000 ranged from 1.3 million to 4.6 million, with an annual incidence ranging from 491 600 to 1.8 million. It is estimated [2] that there are more than 12 million adults with COPD in India with prevalence rates varying depending upon the population studied and the methodology used. In males the prevalence varies from 2.12% to 9.4% in north India and from 1.4% to 4.08% in south India. Similar patterns are reported in women, with lower rates in the south.

The Transplantation of Human Organ Act (THO) was passed in India in 1994.First successful human heart transplantation was done in India by Prof. Venugopal on 3rd of August 1994 at All India Institute of Medical sciences , New Delhi and the first successful single lung transplantation was done by Dr Madhu sankar on 17th of November 2011 at Chennai. The first combined heart and lung transplantation was done by Prof K.M. Cherian on 3rd of May 1999 at Chennai. Since then, over 400 heart transplants and over 50 lung transplants and over 10 combined heart and lung transplants were done in India.

With this slowly increasing experience and as more and more centers and surgeons and physicians are showing more interest in this area, Indian Association of Cardiothoracic surgeons (IACTS) decided to develop some guidelines in this area based on international and some personal experience of the experts in India which will be modified in the coming years with increasing Indian perspective. This is the result of the initial effort.

2. NON-TRANSPLANT SURGICAL OPTIONS FOR ADVANCED HEART FAILURE:

Introduction:

Thrombolysis and PTCA save lives during acute myocardial infarction, but incomplete or delayed reperfusion results in akinesia or dyskinesia. If more than20% of the left ventricular circumference is dyskinetic, the remaining contractile cavity dilates to increase stroke volume. When more than 50% of the myocardium is impaired, increased wall tension (Laplace's law) triggers progressive left ventricular failure [1, 2].

In India, most common cause of heart failure is coronary artery disease, particularly affecting younger patients which is reflective of the ethnic genotypes peculiar to south East Asians. This has resulted in a huge population in its most productive years being afflicted with debilitating symptoms despite maximal tolerated medical treatment.

Most of these patients progress relentlessly to end-stage heart failure (Stage D) necessitating heart transplantation. Heart transplantation has several logistic constraints in terms of donor availability and lack of funds, targets less than 5% of this population. Consequently, treatment options for these patients with advanced heart failure due to ischemic heart disease and idiopathic dilated cardiomyopathy requires a radical re-thinking.

The following account of current and emerging surgical strategies for heart failure concentrates on those patients with left ventricular ejection fraction (LVEF) < 30%, mean pulmonary artery pressure > 25 mm Hg, left ventricular circumferential akinesia or dyskinesia> 60%, and left ventricular end diastolic volume (LVEDV) > 250 ml (LVEDV index(LVEDVI) > 140 ml). Most of these patients are New York Heart Association (NYHA) functional class III or IV with medical treatment.

Revascularization:

In coronary disease the relation between infarct size and mortality has been well defined [3]. Mortality has been clearly found to correlate with the degree of LV dilatation especially the LV end-systolic volume [4].

Non-randomized studies on coronary artery bypass grafting versus medical therapy alone have clearly shown the benefits of CABG on mortality and morbidity [5, 6]

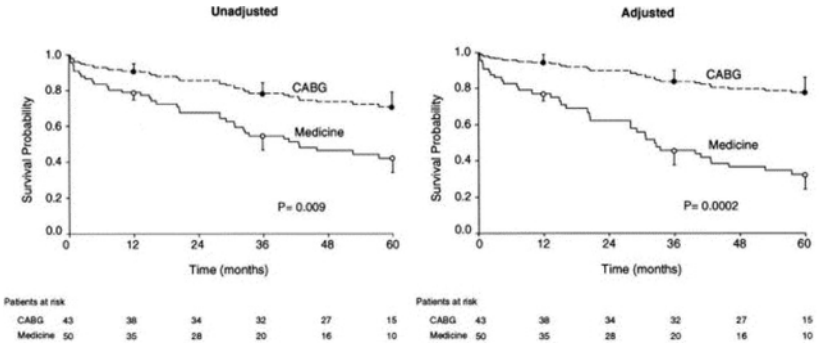

Figure: 1 Plot shows Kaplan-Meier estimated survival probabilities for patients with left ventricular ejection fraction less than 40% treated medically and with CABG. The left panel shows the unadjusted (for baseline prognostic factors) survival estimates, and the right panel shows the adjusted survival estimates.

Clinical non-randomized studies on the benefits of CABG in patients with LV dysfunction clearly demonstrate the need for viability testing by radionuclide studies. Recently cardiac MRI has shown more promise in identifying myocardial viability with more sensitivity and specificity. In patients with severe left ventricular dysfunction and evidence of relatively large areas of viable myocardium, as assessed by PET, had improved long-

term survival with revascularization as compared with medical therapy. This survival benefit was associated with a significant improvement in angina and heart failure symptoms. Long-term surgical survival benefit and symptomatic improvement in patients without evidence of viability was apparent only among those with severe angina [5]. In patients subjected to CABG with LV dysfunction, the 30-day mortality was 5.6% versus 1.1% for patients with normal LV function [6]. The independent risk factors predisposing to mortality in patients with severe LV dysfunction were older age, emergency surgery, mitral incompetence, smoking, respiratory disease, diabetes, cerebrovascular disease, postoperative renal failure, pleural effusion, revascularization without use of LIMA, and prolonged intubation. For mortality benefits of high-risk CABG in this group of patients with LV dysfunction, it is vital to have viable myocardium which on revascularization has the potential to reverse LV dysfunction with contractile recovery. These studies had varied definitions of LV dysfunction with a wide range of LVEF ranging from 20% to 40%.

In patients with myocardial viability and LV dysfunction, there were significant improvements in clinical outcomes after CABG only in patients who had lesser LV dilatation as evidenced by the LV ESV (121±43 versus 153±41 ml, p=0.003) [7]. Although the results of randomized controlled trials are often disappointing and difficult to interpret, there is a paucity of these trials in these patients. The STICH trial was a randomized study designed to determine the benefit of CABG in patients with LV dysfunction due to ischemic cardiomyopathy [8]. These patients were in NYHA class II/III with an LVEF≤35%. Also, most investigators believe that the high crossover rate from medical therapy to surgery in the first year after randomization significantly confounded the interpretation of the STICH study. The post hoc analysis examining treated patients revealed a significant benefit of surgical intervention with respect to overall mortality and freedom from repeat hospitalization. The neutral results of randomized studies provoke the need for further studies. Whereas in the STICH trial, patient selection was flawed by including patients with milder degrees of heart failure which does not allow interpretation of its results for patients with severe LV dysfunction.

CABG in transplant eligible patients:

Transplant eligible patients undergoing CABG were different from the patients with LV dysfunction in terms of the longer duration of symptoms, the presence of right heart failure, and a greater incidence of previous revascularization. Operative risk in the coronary bypass group was significantly higher for those with a greatly increased left ventricular end-diastolic pressure (LVEDP) (> 24 mm Hg), a low preoperative cardiac output (< 2.0 l/min/m2), and for patients in NYHA class IV. Hospital mortality was 7.1% for the coronary artery bypass graft (CABG) patients versus 18.2% in the transplant group. There was no significant difference in hospital mortality in patients with LVEF between 10–20% versus those between20–30%. Survival for the CABG group was78.9% after six years versus 68.9% in the transplant group. Reinvestigation of CABG patients showed a significant decrease in mean (SD) pulmonary artery pressure from 28.2(4.7) mm Hg to 21.2 (3.9) mm Hg ($p < 0.01$).

Pulmonary capillary wedge pressure fell from19.2 (4.3) mm Hg to 13.1 (2.8) mm Hg ($p < 0.01$). Left ventricular ejection fraction improved from a mean of 0.24 (0.03) to 0.39(0.06) ($p < 0.0001$) [9].

In a recent study by Vivek Rao et al [10], they found that patients eligible for transplant had surprisingly favorable mid-term outcomes when subjected to high-risk corrective surgeries. Al these patients had an LVEF < 20% with a VO2 max<14 mL/min/m. The mortality of CABG alone was much lower than CABG with concomitant mitral valve repair or LV restoration (2.3% versus 14%). There was a significant improvement in NYHA class following CABG at mid-term. The multivariable analysis of variables associated with long-term mortality in addition to heart transplant ineligibility were non-ischemic HF etiology, non-elective surgery, higher preoperative creatinine, and longer cardiopulmonary bypass time.

Surgical ventricular restoration:

The palliative surgery based on Laplace's law for ischemic cardiomyopathy with LV aneurysms has seen applicability in large populations. The results of surgical ventricular restoration have been varied, with several factors being responsible.

Rigorous inclusion criteria for surgical inclusion are vital, as is the surgical technique. Large areas of akinesia/dyskinesia of at least 35% of the left ventricle with presence of contractile myocardium is necessary to ensure surgical success [11, 12]. A scarred area of 35%leads to LV dilatation with an LV end-systolic volume (ESV) of 60 ml/m2. Severe pulmonary hypertension is a relative contraindication. This surgery is not applicable to dilated cardiomyopathy and does not have benefits when the akinetic area exceeds 50%. Smaller areas of akinesia of less than25% may not qualify for this procedure [12].

In the largest randomized study comparing revascularization alone and revascularization with surgical ventricular restoration (SVR) conducted in patients with ischemic cardiomyopathy, there was no added clinical benefit of SVR [8]. This study included 1000 patients and was studied worldwide. This trial was severely flawed from its design and inclusion criteria. A large proportion of patients (nearly 66%) did not have LV volume measurements at entry into the study.

Consequently, the SVR procedure may have reflected a small LV plication or limited intracavitary reconstruction. A reduction in LV ESV of 40% is required for clinical success of SVR, whereas in this trial, a reduction of 19% was observed [8]. SVR has also been performed in patients with ventricular tachyarrhythmias and LV aneurysms [13, 14]. Initially, the arrhythmic focus was identified by endocardial mapping. The endocardium was resected and LV endoaneurysmorrhaphy was performed. Ventricular tachyarrhythmias were inducible in very few patients (2out of 25). There was a very low mortality rate both due to sudden cardiac death and congestive heart failure. Blind cryoablation during SVR done at the transition zone had excellent results with recurrence in 2 out of 31 patients, with one of them requiring Intra Cardiac Defibrillator (ICD) implantation.

Hemodynamic characteristics of ischemic cardiomyopathy with left ventricular aneurysms and implications on surgical ventricular restoration:

LV aneurysm formation is dependent on a variety of factors, chief among which is the thickness of the involved myocardium [1]. In anterior aneurysms, the LV apex is maximally involved, as it is thinnest.

This is also the reason LV aneurysms are a sequel of transmural myocardial infarctions rather than subendocardial infarctions. Small aneurysms of less than 11% of the left-ventricular end-diastolic volume (LVEDV) usually do not present with congestive heart failure. When the aneurysmal volume exceeds 15–20% of the LVEDV, it leads to increases in LV end-diastolic pressure, ultimately leading to congestive heart failure. The contractile remote myocardium dilates in order to maintain an effective forward stroke volume. This increases wall stress by the Laplace's law. Although the remote contractile myocardial contraction contributed to systolic ejection, a marked delay was observed in time to peak contraction, while the peak contraction was at least a third less than normal [15]. This has been observed in cardiac magnetic resonance (CMR) studies [15] (Figure 2). The shape of aneurysms has been studied theoretically in a mathematical model, demonstrating a rectangular shape having an increased ratio of active to inactive muscle compared with a circular shape [1]. The hemodynamic characteristics of the LV aneurysm need to be understood in order to plan the surgical strategy.

Surgeons using the techniques of SVR have witnessed a steady evolution over the years, with greater understanding of the underlying pathological substrate. A mere reduction in LV volume may not be sufficient, while an optimal ellipsoid restoration of the LV may seem distant. Recent advances in cardiac imaging technology have enabled study of LV geometry and function.

The intraventricular patch geometry reflects the theoretical calculations in a mathematical model where the ratio of contractile to infarcted muscle was greater with a rectangular aneurysm than a circular one. The patch mimics the aneurysm in this model. The remote or contractile myocardium demonstrated a delay in time to peak contraction with decrease in amplitude of contraction.

The systolic contraction extended into early diastole, while the early diastolic filling was decreased. Following SVR using a rectangular patch, improvements were seen in the remote myocardium with earlier onset of systolic contraction and an increase in the amplitude of contraction.

Following SVR by circular endoventricular patch plasty, significant improvements were seen in the LV basal rotations, while there were no changes in the apical rotations. [16] This demonstrated a greater decrease in LV volume at the base than at the apex, resulting in a less ellipsoid LV configuration.

Modifying the patch geometry to a narrow rectangular one, it was seen that there were significant improvements in both apical and basal LV rotations (Figure 3) [11]. This was also demonstrated in a study by Cirillo *et al*., [17] where a narrow linear patch was used. It has been noted that in smaller LVs, use of a narrow patch may simulate linear repair, while it may be adequate in larger LVs [18].Therefore, patch geometry also needs individualization for the underlying LV geometry for the success of SVR.

SVR is based on Laplace's law of decreasing the LV radius, thereby decreasing wall stress. The success of SVR, though critically dependent on decreases in LVEDV, is further dependent on an optimal restoration of an ellipsoid LV. Restoration of LV rotation is essential for normalization of LV function, as discussed. Decreasing the LVEDV alone does not ensure optimal surgical results, the shape of the restored LV being dependent on the geometry of the endoventricular patch.

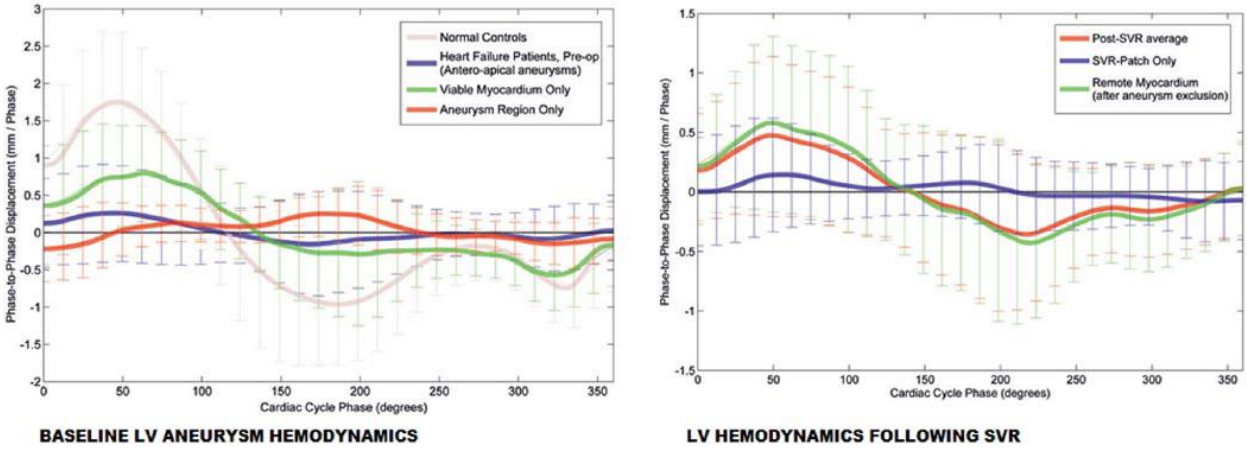

Figure:2 Endocardium-averaged mean myocardial velocity (MMV) characteristics of normal subjects(pink) and patients (blue) are compared against the mean MMV of the aneurysm region alone (red) and that of viable/remote myocardium alone (green), along with standard deviations at each cardiac phase.

Remote endocardium had delayed preoperative peak MMV in comparison with the expectation from the mean normal MMV, and the aneurysm was dyskinetic with the remote myocardium. Endocardium -averaged MMV for patients following SVR (red) are presented alongside regional MMV of the SVR patch (blue) and remote myocardium (green) after optimal aneurysm exclusion by linear endoventricular patch plasty, along with standard deviations at each cardiac phase. Postoperative remote endocardial MMV peaked earlier during the ejection phase of systole than it did preoperatively and, furthermore, had greater magnitude of MMV during early filling at diastole.MMV, mean myocardial velocity; LV, left ventricular; SVR, surgical ventricular restoration. Reproduced with permission from Adhyapak et al.

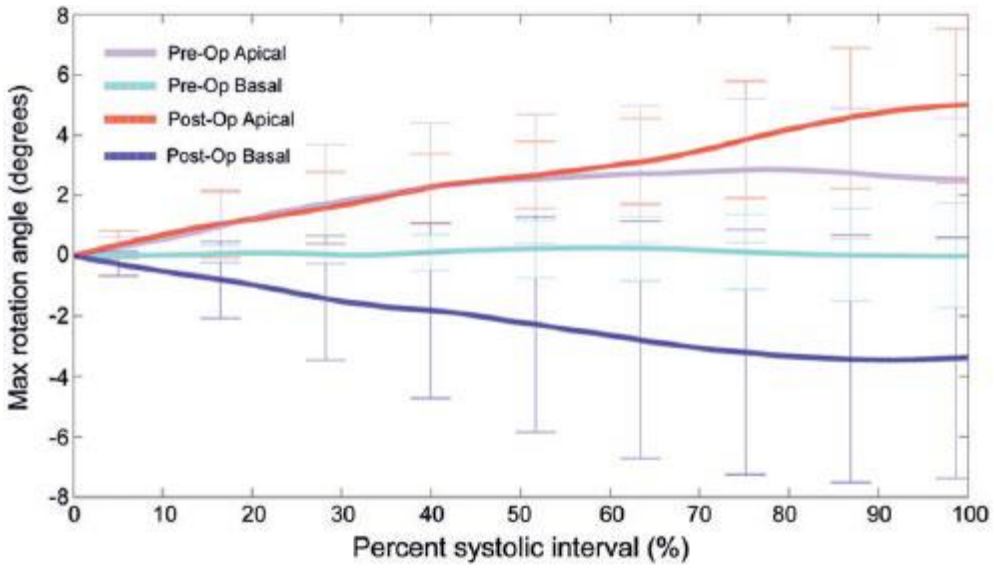

Figure: 3 Maximum anticlockwise (positive), coded light pink, and clockwise (negative) rotation, coded light blue, of the apical and basal slice levels, respectively, during the systolic interval of the cardiac cycle preoperatively. The postoperative rotations are coded red for apical rotation and blue for basal rotation. [Here, anticlockwise direction (apex) is positive and clockwise direction (base) is negative].

Management of mitral regurgitation:

As the failing left ventricle dilates, the papillary muscles are displaced, the coaptation of the mitral valve leaflets is decreased, and a central jet of mitral regurgitation appears. Mitral regurgitation leads to more volume overload of the already dilated left ventricle. Mitral valve repair (or replacement) with preservation of the subvalvar apparatus carries low perioperative mortality, good medium term survival, and symptomatic relief through improvement in cardiac index [19].

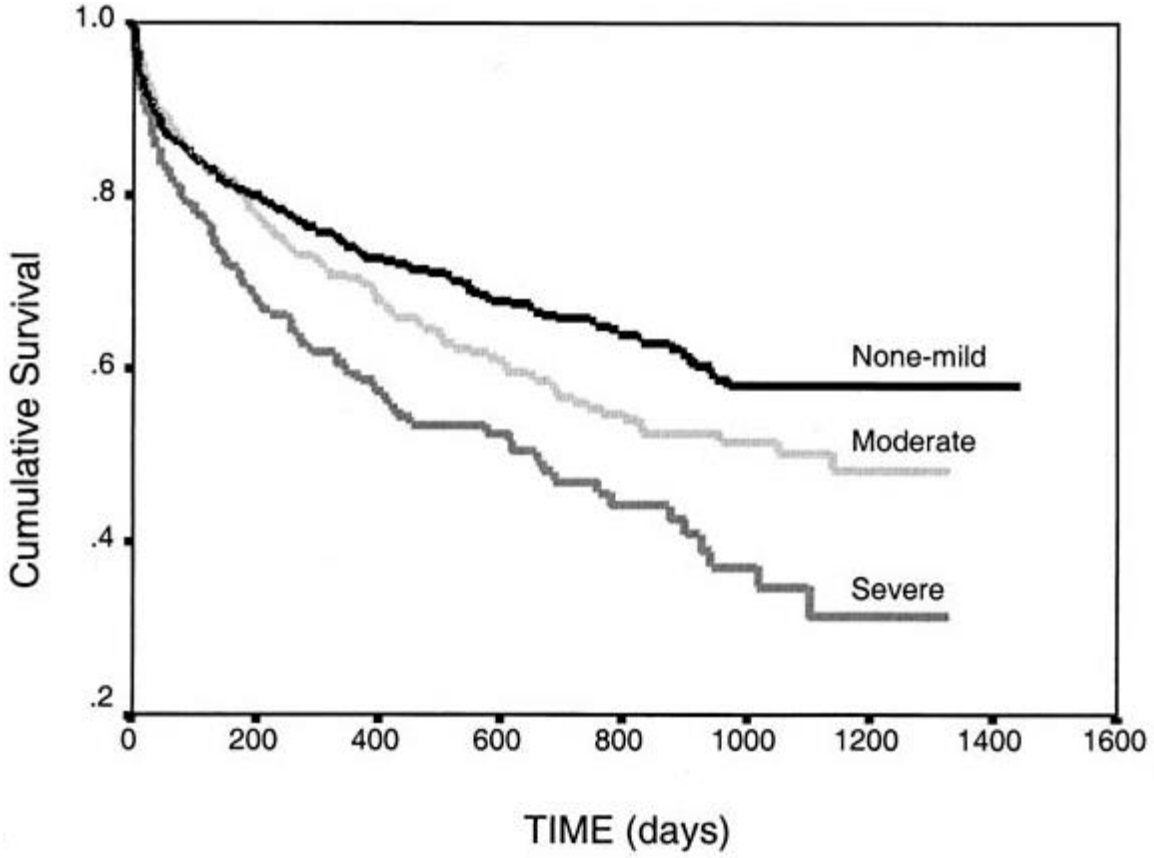

Figure: 4The presence of MR is an independent risk factor of poor outcome in patients with LV systolic dysfunction (LVEF ≤35%)

Mitral valve repair or replacement improves the outlook for heart failure patients in the following situations,

1. Ischemia manifest by angina and variable mitral regurgitation which becomes significantly worse during an acute ischemic episode, causing dyspnoea at rest or left ventricular failure with pulmonary edema.
2. Acute myocardial ischemia or infarction located inferobasally (right coronary or dominant circumflex distribution) which causes sudden posteromedial papillary muscle dysfunction and mitral regurgitation.
3. Acute catastrophic pulmonary oedema caused by papillary muscle rupture (inferobasal in 75% of cases) several days after acute myocardial infarction.
4. Chronic progressive dyspnoea (NYHA III or IV) associated with previous myocardial infarction, an enlarged dysfunctional left ventricle, and varying degrees of pulmonary hypertension. This comprises the largest group.
5. Patients with idiopathic dilated cardiomyopathy and annular dilatation producing moderate to severe mitral regurgitation through inadequate leaflet coaptation.

The recommended threshold for mitral repair in ischemic regurgitation is a left ventricular end systolic volume index > 80 ml/m2 or a calculated regurgitate fraction > 50%of the forward LVEF. Patients with angina, good target vessels, mild to moderate mitral regurgitation, and reversible ischemia posterolaterally on the PET scan can be treated by revascularization alone. Should valve replacement

prove necessary, as much of the subvalvar apparatus as possible should be conserved to maintain left ventricular geometry and function.Division of all chordae tendinae is accompanied by a 47% reduction in LV Emax.

Ischemic mitral regurgitation is a functional problem of unsuccessful coordination of the entire mitral apparatus rather than simple failure of a single papillary muscle. Two techniques have provided symptomatic improvement in this condition. Firstly, mitral annuloplasty with significant under sizing of the valve ring greatly increases leaflet coaptation [21].Systolic anterior motion (SAM) is avoided because of widening of the aorto-mitral angle and increased left ventricular size. The undersized valve ring acutely remodels the base of the myopathic heart, helping to re-establish an ellipsoid shape to the left ventricle. Second, and simpler, is the Alfieri stitch. This can be performed either centrally or towards the side of the ischemic papillary muscle.

Bolling has shown the important effect of mitral repair in patients with end stage dilated Cardiomyopathy [20]. All had severe left ventricular systolic dysfunction with preoperative LVEF ranging from 8–25% (mean 16 %). The average duration of cardiomyopathy was 4years (range 0–16). All patients underwent remodelling ring annuloplasty with an undersized flexible ring. Half had tricuspid annuloplasty. Hospital mortality was < 2% while 12and 24 month survival were 82% and 72%. All

patients were restored to NYHA class I or II with mean postoperative LVEF of 26%. Peak exercise VO2 max rose from a mean of 14.5 to18.6 ml/kg/min. Echocardiography at two years showed a pronounced reduction in sphericity, regurgitant volume, and regurgitant fraction. LVEF, end diastolic and end systolic volumes were all improved.

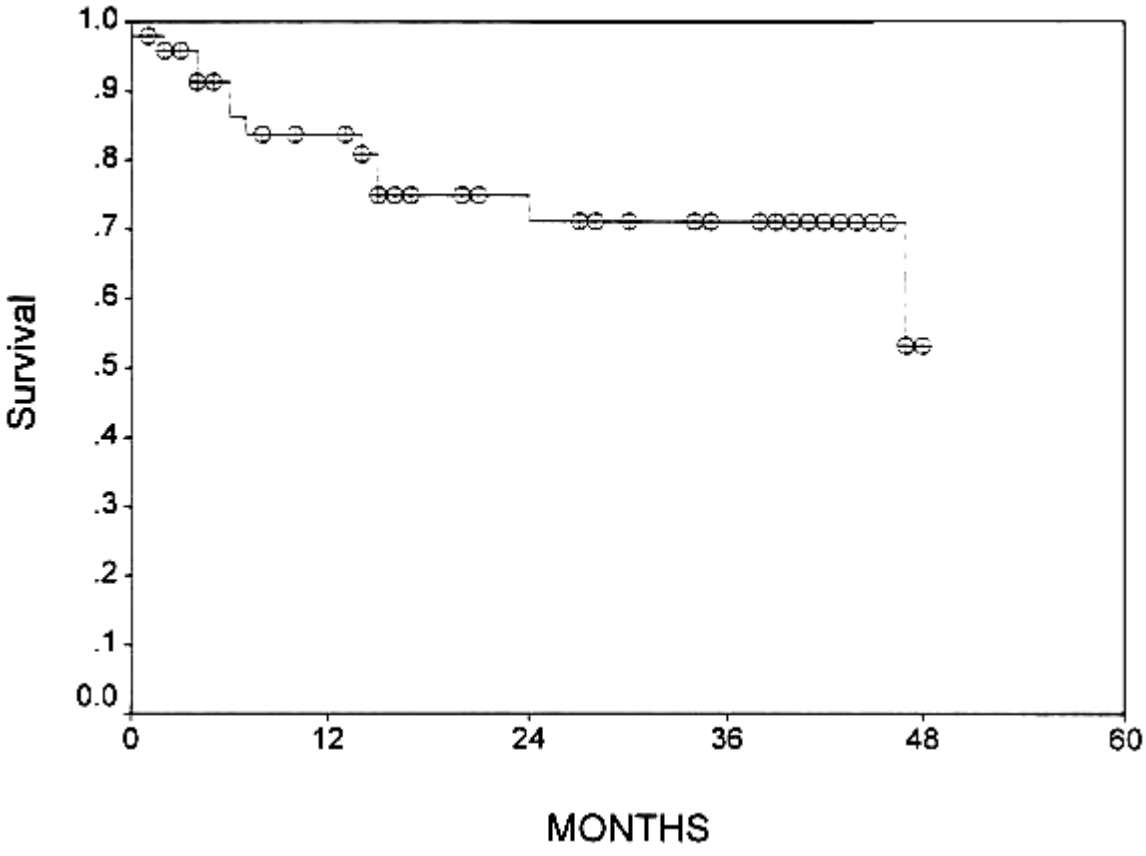

Figure: 5Actuarial survival after mitral valve reconstruction in cardiomyopathy

Left ventricular restraining devices like the acorn cap device and the myosplint device have been disregarded due to lack of clinical benefit although the initial results showed promise in small select samples. Partial left ventriculectomy or the Batista procedure has also been abandoned due to its associated high unacceptable mortality and morbidity.

Summary:

The scope of heart failure surgery is developing rapidly but relies increasingly upon expensive diagnostic techniques and mechanical circulatory support. The major issues are not ethical but economic. In the future, new drugs, gene therapy, and autogenous myocyte culture will promote left ventricular repair during circulatory support, thereby freeing the limited number of donor organs for eligible sicker patients.

3. HOW TO START A THORACIC TRANSPLANT PROGRAMME:

There is no magic formula for starting transplant programme. It is a team game!!!! This fact cannot be over emphasized. This is not for the prima donna surgeon jumping from one hospital to the next, doing 8 coronary artery bypass surgeries in a day .Heart transplant is not a technically difficult operation but is a difficult therapy !!

A few things are very clear how not to start a transplant programme.

1. Doing one or two cases, getting media publicity and then stop
2. Not having a dedicated team
3. Outsourcing the required knowledge to nephrology or other teams

What you need:

1. A leader to drive the programme: the most important point to be noted is the need for a leader with passion for the programme. Very often, we find that the passion is from the hospital management and not the surgeons or the cardiologists. The leader can be a surgeon or cardiologist but he/she needs passion, vision and should be a team builder.

2. A strong mechanical circulatory programme, like extra corporeal membrane oxygenator [ecmo] or short term pumps is crucial as up to 30 % patients become sick awaiting a donor organ, have a cardiac arrest or develop impending renal shut down and need mechanical support. An ecmo system from any reputed vendor will do.

3. Minimum of 2 surgeons needed: one to harvest and the other to implant, preferably alternating. Also, transplants have an annoying habit of organs becoming available on the one day in the month or year when the surgeon is on leave for important personal work and a sick patient is waiting. Therefore more than one person should be able to stitch the heart in.

4. Two dedicated cardiac anesthetists.

5. Again, for managing the donor and recipient, a team of intensivists, either as a part of anesthesia or an independent team they form the backbone of the programme. Heart transplant is nothing but high quality intensive care. They should be capable of initiating ecmo in the ICU, doing oesophageal echo, bronchoscopy, percutaneous tracheostomy, and thoracentesis under echo guidance and insert difficult central lines on ecmo patients under echo/ultrasound guidance. They also should have thorough knowledge of Immunosuppression. They often do the preoperative hemodynamic evaluation as well.

6. Cardiologist: strange that a cardiologist is number 6, but alas that is the reality in India now. Very few are interested. But you need a cardiologist for endomyocardial biopsies, yearly coronary angiogram,

intravascular ultrasound and follow-up of these patients. If they can get interested in the management of these patients, it is ideal as then they can drive the programme and claim ownership.

7. 2 perfusionists: It is crucial. They need to be well versed with ecmo, LVAD and are needed for donor harvesting especially with the increasing use of organ care systems

8. 2 Transplant coordinator / VAD coordinator: their role cannot be over emphasized. They register the patient in the state transplant waiting list, coordinate with the logistics team and medical team during donor organ retrieval and transplant, track donor calls and give the names of the potential recipients to the state authority, collect reports, and blood tests and biopsy results, look after the exit site, the list is endless; they are the backbone of the programme.

9. Logistics team: They have a crucial role: Arrange green corridor, air tickets or air ambulances, know flight timings to most donor airports and often have a working relationship with airline staff, police and airport personnel and air traffic controllers of smaller airports!! Without them long distance procurement is impossible. Arrange accommodation for outstation patients.

10. Laboratory: ideally inhouse, but can be anywhere. Quick turn around time for tests.
Should be able to do drug levels, PCR, flow cytometry, cd levels etc. Capable of immuno histochemistry for antibody mediated rejection (amr) and expert microbiology. Pathology for biopsies can be outsourced if not available in house. Ideally should report on biopsies in a few hours.

11. Blood bank: modern blood bank with all the products.

12. Infection disease specialist: transplant is a complex science with ever present threat of infections .Expert id consult is a must.

13. Clinical Immunologist: In India, this is a luxury, and often the immuno suppression is managed by the surgeon with the critical care team.

14. Dedicated or and ICU nurses

15. Supportive hospital management with a business manager: the stakes are high; bills are high, outcomes not always predictable. Patients can die and bills will shoot up. A separate business manager to coordinate between the treating team and hospital management who understands both sides of the equation is a great help.

16. Important additional equipment:
1. ECMO
2. IABP
3. Cell saver
4. Nitric oxide
5. Vo2 max
6. Dedicated portable echo machine with TEE for donor evaluation.
7. Bronchoscopic equipment with recording for lung transplant
8. Portable blood gas for donor evaluation
9. Cardiac output computer
10. Dedicated CRRT machine

The requirement for a heart transplant program includes the following: Transplant cardiothoracic surgeon, Transplant cardiologist, Transplant coordinators, Nurse practitioners, Physical therapist, Psychologist, Anesthetist, Dietician, Financial coordinator and social worker. They work together to get a program running.

4. INDICATIONS FOR HEART TRANSPLANTATION:

The primary indications for heart transplantation for adult patients have been nonischemic cardiomyopathy (53%) and ischemic cardiomyopathy (38%). Other indications include: valvular heart disease (3%), retransplantation (3%) and others (<1%)

In general, patients with advanced heart failure should be considered for heart transplantation if optimal medical therapy (OMT) as recommended by the ACC/AHA guidelines and electrical therapies including Cardiac Resynchronization Therapy have failed to improve symptoms or halt progression of the underlying pathology and with an expected 1 year mortality exceeding 50 %[1, 2]. Any reversible causes contributing or worsening of the heart failure like electrolyte imbalance, arrhythmias, inadequate dose of diuretics, inadvertent medications like NSAIDS or surgically amenable cardiac conditions like Mitral Regurgitation should be corrected before transplantation evaluation is considered.

An ongoing evaluation for the adequacy of the current medical therapy should be done at all stages. If possible few months of medical stabilization should be considered before contemplating heart transplantation. The above general principles will not be applicable in patients presenting with high INTERMACS score and in those with inability to taper off inotropes.

Indications – Societal Recommendations:

The ACC/AHA guidelines include the following indications for cardiac transplantation [3]

- Refractory cardinogenic shock requiring intra-aortic balloon pump counter pulsation or left ventricular assist device (LVAD)
- Cardiogenic shock requiring continuous intravenous inotropic therapy
- Peak VO2 (VO2max) less than 10 mL/kg per min
- NYHA class of III or IV despite maximized medical and resynchronization therapy
- Recurrent life-threatening left ventricular arrhythmias despite an implantable cardiac defibrillator, antiarrhythmic therapy, or catheter-based ablation
- End-stage congenital HF with no evidence of pulmonary hypertension
- Refractory angina without potential medical or surgical therapeutic options.

The European Society of Cardiology describes a series of features that must be met before consideration for heart transplant which are more specific and include, functional, structural and symptoms parameters[4]. These criteria can be more easily accessed and will be of more practical help.

- Severe symptoms, with dyspnea at rest or with minimal exertion (NYHA class III or IV)
- Episodes of fluid retention (pulmonary or systemic congestion, peripheral edema) or of reduced cardiac output at rest (peripheral hypoperfusion)
- Objective evidence of severe cardiac dysfunction (at least one of the following): left ventricular ejection fraction less than 30%, pseudo normal or restrictive mitral inflow pattern on Doppler echocardiography, high left and/or right ventricular filling pressure severely impaired functional capacity demonstrated by one of the following: inability to exercise, 6-minutewalk test distance less than 300 m (or less in women or patients who are age 75 and older), or peak oxygen intake less than 12 to 14 mL/kg/min
- One or more hospitalizations for HF in the past 6 months.

The traditional classical indications constitute the indications in 95% patients, but in < 5% patients especially in those with HCM/RCM, the following may also to be considered as indications

Persistent haemo-dynamically compromising ventricular arrhythmias, refractory to all usual therapies.

Refractory angina, where there is clear objective evidence of recurrent significant myocardial ischemia that is not amenable to conventional treatment

RCMP/HCM with persisting NYHA III or IV symptoms refractory to conventional treatment and/ or recurrent admissions with decompensated HF, independent of ejection fraction.

Clinical Criteria for India:

In resource limited situations, risk stratification using sophisticated tests like the cardio –pulmonary exercise testing may be of limited clinical relevance. In this situation strict clinical criteria may be useful.

1. ≥ 2 admission for treatment of ADHF within the last 12 months
2. Persistent clinical evidence of overt HF after OMT
3. Calculated SHFM score indicating a >20% 1-year mortality
4. Along with Echo evidence of RV dysfunction or increasing PAP on optimal treatment
5. Along with anemia, involuntary weight loss, liver dysfunction or hyponatraemia attributable to HF
6. Along with deteriorating renal function attributable to HF or inability to tolerate diuretic dosages sufficient to clear congestion without change in renal function
7. With Significant episodes of ventricular arrhythmia despite full drug and electrophysiology/device treatment

The above clinical criteria should be used by the clinician for prompt referral for transplant

Tools for Risk Stratification:

Tools to improve risk stratification of HF patients are critical to ensure that only patients with a high probability of benefit are subjected to the risks of heart transplant. In patients with HF, several methods are typically employed to objectively estimate adverse prognosis with medical therapy alone.

Exercise capacity as assessed by peak VO2 (VO2max):

Exercise capacity as assessed by VO2max is a dynamic objective variable that assesses cardiac reserve and peripheral adaptations to a reduced cardiac output much more accurately than NYHA classification. It is generally considered the gold standard for establishing a severity of functional cardiac Impairment that merits active consideration for transplant.

Patients with compensated CHF and a peak oxygen consumption of less than 14 mL/kg or <50% predicted are considered sufficiently impaired for transplantation [(5)]. This approach suggests that cardiac transplantation can be safely deferred in ambulatory patients with severe left ventricular dysfunction and a peak oxygen consumption of greater than 14 mL/kg/min. With the current evidence based HF therapy including beta-blockers, spironolactone, angiotensin converting enzyme inhibitors and devices(i.e., implantable cardioverter-defibrillator and cardiac resynchronization therapy), a VO2max ≤10 mL/kg/min rather than the traditional cutoff value ≤14 mL/min/kg may be more useful for risk stratification in the device era[(6).] More recent studies have suggested that ventilator efficiency (VE/VCO2) may be a more powerful prognostic factor than VO2Max [(7)]. This may be more useful in patients with inadequate peak respiratory exchange ratios (RERs), a measure which is used to confirm that the patient has achieved anaerobic threshold. This parameter is independent of body mass index, another confounding factor that can limit the interpretation of Vo2 max.

Cardiopulmonary exercise testing is a relatively specialized test, and is not routinely available outside of transplant centers. It would also be expensive and impractical to screen all HF patients with full exercise testing

Heart Failure Survival Score (HFSS):

The predictors of survival in the HFSS include:
- Presence or absence of coronary artery disease;
- Resting heart rate;
- Left ventricular ejection fraction;
- Mean arterial blood pressure;
- Presence or absence of an intraventricular conduction delay on ECG;
- Serum sodium;
- VO2max.

Scores are categorized into low-risk, medium-risk, and high-risk. Patients in medium and high-risk groups (1-year survival of 72% and 43%, respectively) are most likely to die or require urgent transplant in the following year; they should be considered for cardiac transplantation. Transplantation can be safely deferred in patients in the low-risk group (1-year survival 93%) [8].

The Seattle Heart Failure Model (SHFM):

This model is based on age, sex, NYHA class, weight, ejection fraction, blood pressure, medications, a few laboratory values, and other clinical information [9].Furthermore, the model has incorporated the impact of newer HF therapies on survival, including ICDs and CRT. The model provides an accurate estimate of 1-, 2-, and 3-year survival with the use of clinical, pharmacologic, device, and laboratory characteristics. SHFM was developed in an ambulatory HF population and there has been concern that it may overestimate survival in the advanced HF population [10]. Nevertheless, it remains a useful method for estimating survival in HF patients

The Index for Mortality Prediction After Cardiac Transplantation (IMPACT) score was recently developed and noted to predict short- and long-term mortality after heart transplant [11].

Contraindications [1, 3, 12]:

Even though the literature mentions a large number of contraindications, they should not be considered sacrosanct but should think of exclusionary considerations

Pulmonary Hypertension: Irreversible fixed pulmonary hypertension with maximal medical and mechanical therapy. In general, acceptable candidates will have demonstrable sPAP< 50, Trans Pulmonary Gradient ≤ 15 mmHg, and a PVR -< 3-4 wood units.

Irreversible End Organ Damage (liver, kidney, cerebrovascular): Considered an absolute contraindication unless multi-organ transplant is considered. The respective specialty doctors should be contacted.

Irreversible Pulmonary Disease: FVC < 50% of predicted will be considered an absolute contra indication. FEV1 %/FVC < 0.6 will be considered a relative contra indication after the pulmonologist has been consulted.

Peripheral Vascular Disease: Severe symptomatic disease irremediable to surgical intervention will be exclusionary.

Malignancy: A history of malignancy will be evaluated on the basis of likelihood of recurrence, likelihood of metastases, and overall survivability from the tumor.

Uncontrolled Major Affective Disorders or Schizophrenia: Likelihood to adversely affect compliance will be considered a relative contraindication.

Substance Abuse: Active alcoholism or active use of drugs of abuse/ nicotine is considered exclusionary unless behavioral change/treatment is documented.

Obesity: Obesity with a euvolemic BMI >35 is a relative contraindication.

Osteoporosis. Significant osteoporosis will be considered a relative contraindication

Noncompliance. History of documented significant medical noncompliance will be considered exclusionary unless behavioral change is documented.

Psychosocial Status. Psychosocial or financial issues that could result in inadequate post-transplant care are considered a relative contraindication.

HBsAg + and Hepatitis C AB + are relative contraindication and should be further evaluated for the level of active viremia and for liver cirrhosis.

HIV infection – Active HIV infection is an absolute contraindication, but some of the transplant centers in USA and Canada do transplants from HIV positive donors.

Old age - Once considered an absolute contraindication to transplantation, older recipient age is now seen as a relative contraindication [13].

5. PRE-OP EVALUATION FOR HEART TRANSPLANTATION:

The Heart Transplant evaluation process is carried out by a transplant team. The team includes a transplant surgeon, a transplant cardiologist, one or more transplant nurses, a social worker, and a psychiatrist or psychologist along with specialists from various departments as deemed necessary.

Components of the transplant evaluation process include the following:

- psychological and social evaluation: Psychological and social issues involved in organ transplantation, such as stress, financial issues, and support by family and/or significant others are assessed. These issues can significantly impact the outcome of a transplant.
- Blood tests: Blood tests are performed to help determine a good donor match and to help improve the chances that the donor organ will not be rejected.
- Diagnostic tests: Diagnostic tests may be performed to assess the lungs as well as the overall health status. These tests may include X-rays, ultrasound procedures, computed tomography (CT scan), pulmonary function tests, and dental examinations. Women may receive a Pap test, gynecology evaluation, and a mammogram.
- Other preparations: Several immunizations will be given to decrease the chances of developing infections that can affect the transplanted heart.

The detailed test protocol is described below:

Unless critically ill, all patient will have the following tests as the part of the evaluation for transplant.

1. Routine laboratory studies (Metabolic profile, liver function tests, thyroid function tests, cholesterol profile, complete blood count and differential, sedimentation rate, prostate specific antigen, iron studies, PT/PTT, hemoglobin
2. Serologies for hepatitis B, hepatitis C, EBV, CMV, HSV, VZV, toxoplasmosis
3. HIV testing
4. PPD skin testing with controls

5. Echocardiography and/or MUGA scan
6. Electrocardiogram
7. Cardiopulmonary stress testing with max VO2 measurement

8. Right heart catheterization with measurement of pulmonary vascular resistance. If likely cardiac cirrhosis in patients with chronic right heart failure especially with elevated right atrial pressures and enlarged liver and ascites, if the fibrascan is showing a high reading (keeping in mind that it will be high in heart failure), then a transjugular or transfemoral hepatic vein wedge and free hepatic vein gradient can be taken. If the gradient is more than 5, it predicts a likely change of future cirrhosis and a combined liver and heart transplant should be considered. Also a transjugular liver biopsy with more than 25% fibrosis also suggests a similar approach.

If the PA pressures (PA systolic > 50, PVRI >3) are high along with a high transpulmonary gradient > 12, reversibility can be tested on table or by decongestion and repeating the test after some time.

Right heart pressures every six months.

9. Pulmonary function tests
10. Chest radiograph
11. 24 hour urine collection for creatinine clearance and total protein
12. Prostate specific antigen (men >45 yrs); mammogram and Pap smear (women > 40 years)

13. Panel reactive antibody (PRA) (mandatory) and HLA phenotype (not mandatory). Send PRA before vaccination. Done every six months if on waiting list.

For patients 50 or older and all patients with diabetes:

1. Abdominal ultrasound
2. Carotid and transcranial dopplers
3. Non-invasive arterial studies (for ABI)
4. CT chest, head, abdomen is often done as a baseline
5. CEA levels.

Consultations will be obtained from the following services:

1. Psychiatry
2. Social work
3. Other clinical services (eg, renal, pulmonary, ID, GI, etc. as needed)

- <u>TRANSPLANT WORKUP LIST (RECIPIENT)</u>

<u>Basic Blood Tests</u>

Blood Group
Hb
TLC
DLC
Platelets
BT,
CT, PT
Blood Urea
S. Creatinine
S. Protein, AG Ratio
Sodium, Potassium, Calcium
SGOT, SGPT
SALK PHOS
S. Bilirubin, Direct, Indirect
Thyroid Function T3, T4, TSH

Other Lab Test
Urine r/m
Urine 24hrs. creatinine
and Cr. clearance

Stool r/m
ECG

Imaging
Chest X-ray
CT Chest – non contrast
MRI Brain / CT head if any Implant.
Carotid Doppler
Ultrasound Abdomen

CULTURE	PROCEDURES	SAMPLE
Urine Culture c/s	Use sterile container	Send at micro-biology lab
Stool culture	Use sterile container but only patients with diarrhea	--do--
Blood culture aerobics	Use sterile container. sample quantity- 2ml.	--do--
B/L groin culture c/s – aerobic and fungal	Sterile swab, moist with N. Saline, Stroke 4 times over area (2) send in a sterile tube 2	--do--
B/L axilla culture – aerobic and fungal	--do--	--do--
B/L cubital fossa – aerobic and fungal	--do--	--do--

Consultations	Procedures
Gastroenterology +/- endoscopy	send consult after d/w primary consultant
Renal	--do--
Dental	--d0--
Psychiatry	--do--
Gynae (females) + Pap smear	--do--

Echocardiogram
Catheterization

Vaccinations
Hepatitis B
Pneumococcal
H influenza
DPT, Mumps, Measles (Complete if incomplete)

SEROLOGY	PROCEDURE
Hbsag	--do—
Anti HBs	--do—
Anti HBc	--do—
Anti HCV	--do—
HIV 1,2	--do—
CMV	--do—
HSV	--do—
TOXOPLASMA	--do—

6. IMMUNOSUPPRESSION AFTER HEART TRANSPLANTATION:

Introduction:

Immunosuppression after solid organ transplantation is important for graft survival. In spite of improved therapeutic strategies, the adverse effects associated with these agents and the risks of long-term immunosuppression present a number of challenges for the clinician. In the early 1960s, 6-mercaptopurine (Purinethol) followed by azathioprine (Imuran) immunosuppression became the standard of care. Beginning in 1962, it became possible to closely match donor and recipient tissue. After the first initially successful series of transplantations performed between 1962 and 1964, the combination of azathioprine and steroids came into widespread use and became part of the primary immunosuppressive regimen.

Principles of immunosuppression:

The immune response to transplantation is highly dependent on T cell activation and proliferation. Many of the current immunosuppressive drugs target specific intracellular pathway of T cell activation.

Optimal immunosuppression during postoperative period should include triple therapy of steroids, calcineurin inhibitor and myelosuppressive agents. Recipient should be started on calcineurin inhibitors as early as possible after end organ function improves. If renal dysfunction does not resolve sufficiently, Basiliximab can be used as bridge to CIN; alternatively sirolimus can be used after complete wound healing. Maintenance therapy generally consists of combination therapy with antiproliferative agents, a calcineurin inhibitor, and steroids. Maintenance regimens are evolving with efforts to diminish the nephrotoxicity of calcineurin inhibitors and metabolic toxicity of steroids. Thus, some regimens may add TOR inhibitors to lower doses of calcineurin inhibitors or to eliminate calcineurin inhibitors or steroids.

Immunosuppressive agents:

A. Induction agents:
1. Methyl prednisolone
2. Antithymocyte Globulin
3. Basiliximab

B.Maintenance Therapy:

1. Calcineurin inhibitor
   - Tacrolimus
   - Cyclosporine
2. Anti-proliferatives
   - Mycophenolate mofetil
   - Azathioprine
3. m-TOR Inhibitors
   - Sirolimus
   - Everoimus

4. Corticosteroids
   - Prednisolone.

C. Antirejection therapies.

1. Methylprednisolone.
2. Intravenous Immunoglobulin
3. Rituximab
4. Bortezomib
5. Eculizumab

Corticosteroids:

Corticosteroids used as both induction and maintenance immunosuppression. The most common corticosteroids used in transplantation are oral prednisolone and intravenous methyl prednisolone. These agents are metabolized by the liver and excreted by the kidneys as inactive metabolites. Drug interactions with P450 inhibitors and inducers are common.

After entering target cell, corticosteroids bind to intracytoplasmic receptors and this steroid-receptor complex migrate into nucleus, where it retards gene transcription resulting in inhibition of expression of interleukin-2 and other cytokines like IL-1,IL-3,IL-6 and TNF –Alpha. Other functions include suppression of macrophage function, reduction in adhesion molecule function and inhibition of leukocyte transmigration.

Adverse effects of corticosteroids include cushingoid features, osteoporosis, avascular necrosis, cataracts, glucose intolerance, infections, hyperlipidemia, hypertension, peptic ulcer disease, pancreatitis, bowel perforation, weight gain, psychiatric disturbances, and growth restriction.

Data from the latest International Society of Heart and Lung Transplantation (ISHLT) Registry show that 73% of HT recipients remain on CSs at 1 year. Several studies indicate that it is both feasible and safe to wean most patients from CSs by 6 to 12 months after HT[2]. Reduction and discontinuation of CSs is desirable because it lowers the long-term adverse effects of these drugs. Experience in India suggests that low dose should continue lifelong.

Calcineurin inhibitors:

Cyclosporine:

This agent is used for maintenance immunosuppression. It is a polypeptide of 11 amino acids of fungal origin and a prodrug that binds to cyclophilin; complex inhibits calcineurin phosphatase and T-cell activation by dephosphorylation of inactive nuclear factor of activated T cells (NF-AT). Therefore, it prevents the production of IL-2 via calcineurin inhibition.

Adverse effects of cyclosporine include nephrotoxicity (immediately secondary to renal ischemia, after 2-3 weeks after transplantation, secondary to renal vasoconstriction; and chronic, secondary to interstitial nephritis). Other adverse effects include hyperkalemia, hypomagnesaemia, nausea, vomiting, diarrhea, hypertrichosis,

hirsutism, gingival hyperplasia, skin changes, hyperlipidemia, glucose intolerance, infection, malignancy, hyperuricemia, and hemolytic uremic syndrome. CYA is absorbed mainly in the upper portion of the GI tract. Because the renal excretion of CYA is only 6%, the drug is not appreciably removed by hemodialysis. Metabolism of CYA occurs via the cytochrome P-450.

Initial oral dose – 25-50 mg bid and, if renal function remains normal, rapidly increase over 4-5 days to achieve whole blood trough levels of 300-400 ng/ml.

Months post-transplant	Target level ng/ml
0-3	350-450
3-6	250-350
6-12	200-300
>12	100-200

Currently, pre-dose 'trough' concentration (C0) is being used, but there is sufficient evidence for C2 levels that this correlates with clinical outcome or with drug exposure. Recent research has shown that CsA exposure measured at C2 is a good predictor for outcome in transplant patients.

Tacrolimus:

Tacrolimus is a macrolide antibiotic and is active against helper T cells, preventing the production of IL-2 via calcineurin inhibition (binds to tacrolimus-binding protein instead of cyclophilin protein). The tacrolimus: FKBP12 active complex inhibits calcineurin with greater potency than the corresponding cyclosporine complex. This agent is used for maintenance immunosuppression and for rescue therapy in patients with refractory rejection under cyclosporine-based therapy.

Adverse effects are similar to those of cyclosporine but with a lower incidence of hypertension, hyperlipidemia, skin changes, hirsutism, and gum hyperplasia and a higher incidence of new-onset diabetes mellitus after transplantation (NODAT) and neurotoxicity. Although tacrolimus causes less cosmetic effects than cyclosporine, it can cause reversible alopecia. Glucose tolerance appears to be dose related .10-30 % of patients require temporary insulin therapy dose reduction leads to resolution.

Drugs which affect with cyclosporine levels will also likely affect tacrolimus as both cyclosporine and tacrolimus undergoes metabolic degradation primarily through the hepatic cytochrome p-450.

Phase III trial conducted in Europe and US did not show a significant difference between tacrolimus and cyclosporine in the incidence of severe rejection or hemodynamic compromise rejection requiring treatment within the first 6 months post-transplant (22% vs. 32%), but did show a significant difference in the incidence at 1 year (23% vs. 37%). In phase III trials, 1-year patient survival was similar between tacrolimus and cyclosporine recipients in the EU (93% vs. 92%) and the US (95% vs. 90%). Tacrolimus was shown to be effective in the prevention of rejection in pediatric and African American heart transplant recipients. The tolerability profile of tacrolimus in heart transplant recipients was broadly similar to that of cyclosporine, although tacrolimus was usually associated with lower incidences of post-transplant hypertension and dyslipidaemia.[3]

Initial oral dose – 1-2 mg bid and, if renal function remains normal, rapidly increase over 4-5 days to achieve whole blood trough levels of 8-12 ng/ml.

Months post-transplant	Target level ng/ml
0-3	7-12
3-6	8-9
6-12	6-8
>12	5-8

mTOR inhibitors:

Sirolimus:

It is produced by the bacterium *Streptomyces hygroscopicus* and was isolated for the first time in 1972 by SurendraNath, Sehgal and colleagues from samples of *Streptomyces hygroscopicus* found on Easter Island.

Sirolimus, also called rapamycin. This agent is used for maintenance immunosuppression and chronic rejection. Everolimus is a rapamycin analog with a similar mechanism of action and adverse effect profile.

The mode of action of sirolimus is to bind the cytosolic protein-FKBP12 in a way similar to tacrolimus.

Sirolimus can also be used alone, or in conjunction with a calcineurin inhibitor (such as tacrolimus), and/or mycophenolate mofetil, to provide steroid-free immunosuppression regimens. Impaired wound healing and thrombocytopenia are possible side effects of sirolimus. Its antiproliferative and antimigratory actions above and beyond modulation of B-cell and T-cell function make it a particularly unique immunosuppressant. Sirolimus also may alter the long-term consequences of renal dysfunction and malignancy by obviating the need for CNI therapy.

Sirolimus use from the time of transplantation approximately halved the number of patients experiencing acute rejection. The measurable development of transplant vasculopathy at 6 months and 2 years in patients receiving azathioprine was not observed in patients receiving sirolimus.[4]

Dose: 5 mg/day PO if >40 kg and 1 mg/m²/day if <40 kg on day 2 and thereafter; obtain trough levels between days 5 and 7

Dose adjustments: Dose should be adjusted to maintain trough concentrations 8-12ng/ml range based on clinical state and concomitant therapy; further dose adjustment should not be done sooner than 7-14 days following a dose adjustment.

Everolimus:

Everolimus is an immunosuppressive agent used for the prophylaxis of acute rejection after kidney transplantation. Everolimus inhibits the activity of the serine/threonine kinase mammalian target of rapamycin (mTOR), a key enzyme that controls cell growth and metabolism, producing cell cycle arrest from the G1 to S phase. As a consequence, everolimus has antiproliferative and antineoplastic effects. Everolimus is a drug with a narrow therapeutic index. Everolimus may have a role in heart transplantation, as it has been shown to reduce chronic allograft vasculopathy in such transplants. It also may have a similar role to sirolimus in kidney and other transplants. [17]

Everolimus is indicated for low- to moderate-risk de novo heart transplant candidates. There are no conclusive studies thus far indicating that everolimus can be used in high-risk patients, such as sensitized patients and retransplants. Everolimus can also be used as a conversion strategy, mainly to preserve renal function and to manage patients with malignancy. There is no definition of the ideal strategy for conversion, i.e., abrupt or sequential, initial dose of everolimus, or target therapeutic trough blood concentrations. Intensive monitoring is recommended after conversion, especially for acute rejection Recommended initial dose of Everolimus is 0.75 mg twice daily, adjusted to maintain blood trough concentrations of 3–8 ng/m.

Pharmacodynamic Interactions of CSA/TAC/ Sirolimus:

B) Drugs that INCREASE CSA/TAC/ Sirolimus levels			
Antimicrobial: ▪Erythromycin, Clarithromycin ▪Azole Antifungals Fluconazole, Ketoconazole, Itraconazole, Posaconazole, Voriconazole.	↓CSA/TAC/sirolimus metabolism,↑rate of absorption,↓volume of distribution Delayed / major ↓CSA/TAC/sirolimus metabolism Delayed/ moderate	↑CSA/TAC/sirolimus levels, ↑risk of toxicity	Monitor CSA/TAC/sirolimus levels following addition, dose change or discontinuation. Monitor serum creatinine

Antidepressants: Fluoxetine, Fluvozamine>> Sertraline, Menlafaxine, Mirtazapine, Paroxetine	↓CSA/TAC/sirolimus metabolism Delayed/ moderate	↑CSA/TAC/sirolimus levels, ↑risk of toxicity	Consider another antidepressant (citalopram, escitalopram) and/or monitor CSA/TAC/sirolimus levels closely
Cardiovascular: ▪Diltiazem, Verapamil ▪Amiodarone	May inhibit hepatic metabolism of CSA/TAC/sirolimusDelayed / Major	↑CSA/TAC/sirolimus levels, ↑risk of toxicity	Monitor CSA/TAC/sirolimus levels following addition, dose change or discontinuation.

Drug	Proposed Mechanism and Possible effects	Management
amino glycosides, amphotericin B, NSAIDS, C0X-2 inhibitors (CSA and tacrolimus ONLY)	Additive nephrotoxicity	These drugs should be avoided in transplant recipients due to increased nephrotoxicity. The only exception is when the benefit clearly outweighs the potential risks and only used for short-term treatment. Renal function should be monitored closely while these drugs are used with cyclosporine or tacrolimus.
HMG-CoA Reductase Inhibitors: Example: lovastatin, simvastatin, atorvastatin	CSA/TAC/sirolimus may↓metabolism of these agents →accumulation of statin and toxicity Myalgia, myopathy, rhabdomyolysis	Start with low dose of these agents and monitor very closely for toxicity
Digoxin	↓volume of distribution of digoxin by 50-70%, ↑digoxin half-life by 30-40%, and increased digoxin levels Digoxin toxicity such as vomiting, cardiac arrhythmia's	Initiate low dose and follow up with serum digoxin levels Closely monitor for symptoms of digoxin toxicity
Nifedipine phenytoin (cyclosporine ONLY)	Additive incidence of gingival hyperplasia with CSA (not tacrolimus) Incidence increases from 8% (CSA alone) to 51% (combination)	Avoid long term use if possible. Good dental/oral hygiene with regular dentist visits

Anti-proliferatives:

Mycophenolate acid:

It was initially marketed as the prodrug mycophenolate mofetil (MMF) to improve oral bioavailability. More recently, the salt mycophenolate sodium has also been introduced. Mycophenolate mofetil marketed under the trade name CellCept and mycophenolate sodium as Myfortic, inhibit the enzyme inosine monophosphate dehydrogenase (IMDH; required for guanosine synthesis) and impairs B- and T-cell proliferation, sparing other rapidly dividing cells (because of the presence of guanosine salvage pathways in other cells). This agent is used for maintenance immunosuppression and chronic rejection.

Adverse effects include nausea, vomiting, diarrhea, leucopenia, anemia, and thrombocytopenia.

The choice of immunosuppression has an impact on the incidence of CAV (coronary artery vasculopathy). In terms of prevention of CAV, MMF is superior to Azathioprine in either combination. A trend toward improved survival in MMF patients was noted in clinical trials. It can be replaced with azathioprine if diarrhea persists.

In a randomized active-controlled trial of mycophenolate mofetil in heart transplant recipients, Mycophenolate Mofetil Investigators found that survival and rejection were similar in enrolled patients (MMF, n=327; azathioprine, n=323). In treated patients (MMF, n=289; azathioprine, n=289), the MMF group compared with the azathioprine group was associated with significant reduction in mortality at 1 year (18 [6.2%] versus 33 deaths [11.4%]; P=0.031) and a significant reduction in the requirement for rejection treatment (65.7% versus 73.7%; P=0.026). There was a trend for fewer MMF patients to have > or = grade 3A rejection (45.0% versus 52.9%; P=0.055) or require the murine monoclonal anti-CD3 antibody or antithymocyte globulin (15.2% versus 21.1%; P=0.061). Opportunistic infections, mostly herpes simplex, were more common in the MMF group (53.3% versus 43.6%; P=0.025).[5]

Target Mycophenolic acid Trough level >1.5 mg/l. Routinely blood levels are not monitored instead total counts should be monitored to adjust the dose.

Adult dose -Mycophenolate mofetil as CellCept (MMF) -1000 mg bid
Mycophenolate sodium as Myfortic 720 mg bid

Azathioprine:

It was the first immunosuppressive agent used in organ transplantation and provided a share of the 1988 Nobel Prize to its developers. It is an antimetabolite prodrug that converts 6-mercaptopurine to tissue inhibitor of metalloproteinase, which is converted to thioguanine nucleotides that interfere with DNA synthesis. Other possible mechanism includes converting co-stimulation into an apoptotic signal. It is used for maintenance immunosuppression; however, it became a second-line drug after cyclosporine was introduced.

Adverse effects of azathioprine include leukopenia, thrombocytopenia, and liver toxicity. Azathioprine is listed as a human carcinogen in the 12th Report on Carcinogens by the Program of U.S. Department of Health and Human Services, asserting that it is "known to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in humans.[6]Myelosuppression becomes a serious problem when used with allopurinol ,myelosuppression can improve with drug discontinuation. The dose of azathioprine should be decreased when administered with allopurinol and when withdrawing steroids. Complete blood cell counts and pancreatic and liver enzyme levels must be monitored.

Azathioprine is compatible with cyclosporine and tacrolimus. Azathioprine use in transplantation has been replaced by mycophenolate mofetil in many transplant centers.

Adult dose: 100 mg bid adjust effective therapeutic dose by monitoring total count

Biological agents:

Biologic agents are polyclonal and monoclonal antibodies and are frequently used in transplantation for induction immunosuppression or treatment of rejection. The 3 antibodies used for induction therapy are the lymphocyte-depleting agents: (1) antithymocyte globulin, (2) alemtuzumab, and (3) basiliximab, which is nondepleting. Historically, immunosuppressant selection was based solely on efficacy for the prevention of rejection. In the current era of transplantation, it is now common practice in the transplant community to select induction therapy based on risk-benefit considerations for each patient.

Polyclonal antibodies (antithymocyte globulins):

Antithymocyte globulins have been used commonly for induction immunosuppression and treatment of acute rejection in solid organ transplantation. These agents are derived by injecting animals (rabbit or horse) with human lymphoid cells, then harvesting and purifying the resultant antibody. Polyclonal antibodies induce the complement lysis of lymphocytes and uptake of lymphocytes by the reticuloendothelial system and mask the lymphoid cell-surface receptors. Preparations include

1. Horse antithymocyte globulin.

2. Rabbit antithymocyte globulin.

Although ATG is the favored agent, equine preparations have historically been used.

Most regimens involve 5-7 days of intravenous administration of thymoglobulin for induction immunosuppression or treatment of corticosteroid-resistant rejection or antibody-mediated rejection.

Thymoglobulin is a polyclonal, in conjunction with inhibitors of terminal complement activation, it has been shown to be beneficial in cross-match–positive transplantation. Thymoglobulin possibly provides better protection against acute rejection and improves patient and graft survival. Found to have more CMV infection and post transplantation malignancy. In contrast, data from a registry that included 25,000 transplant patients failed to reveal such association. Thymoglobulin causes leukocyte depletion with a greater delay to recover. Of special importance is adding antiviral therapy to the treatment regimen of patients who receive antithymocyte globulins as induction therapy.

As polyclonal agents are xenogenic proteins, adverse effects include fever and chills. Other adverse effects are thrombocytopenia, leucopenia, hemolysis, respiratory distress, serum sickness, and anaphylaxis. Thymoglobulin rarely causes adult respiratory distress syndrome. Some adverse effects are ameliorated with steroids, acetaminophen, and diphenhydramine. A high average dose of antithymocyte immunoglobulin has been associated with an increased risk of non-Hodgkin lymphoma.

Thymoglobulin administration is associated with coagulopathy. Using an international normalized ratio screening protocol and an aggressive transfusion protocol, bleeding complications associated with coagulopathy can be avoided in this higher-risk group.

Polyclonal antibodies are used for induction and for the treatment of steroid-resistant rejection in heart transplant recipients. Both ATGAM and Thymoglobulin have Food and Drug Administration (FDA) approval for the management of acute rejection in renal transplant recipients. The few comparisons between ATGAM and Thymoglobulin appear predominantly in the renal transplantation literature. From the limited data available, Thymoglobulin appears to be moderately more efficacious than ATGAM when used for induction therapy or for treating steroid-resistant rejection.[7, 8]

Currently, rATG dosing in heart transplantation is largely empiric and there is a wide variation in protocols. Generally, doses are lower than in the past, with few centers administering total doses >7.5 mg/kg and some centers giving only a single dose of 1 mg/kg/day or a cumulative dose of 3.5 mg/kg in total. Studies of outcomes associated with different dosing strategies are urgently required.

Interleukin-2 Receptor Antagonist-Monoclonal anti-CD25 antibody:

Basiliximab:

Basiliximab (Simulect) & declizumab are humanized antimonoclonal antibodies that target the IL-2 receptor (CD25). These agent bind to the IL-2 receptor α-chain (CD25 antigen) on activated T cells, depleting them and inhibiting IL-2–induced T-cell activation.

These agents have a very low prevalence of adverse effects, although hypersensitivity reactions have been reported with basiliximab, Induction treatment with basiliximab requires 2 doses, and no monitoring is required.

One small trial randomized 55 heart transplant recipients receiving prednisone, mycophenolate mofetil, and cyclosporine to daclizumab or no additional therapy.[9] During the induction period (3 months), acute rejection, defined as an endomyocardial biopsy grade of ≥2, was decreased from 63% to 18% (*P*=0.04). Mortality was not different. The need for anti-lymphocyte therapy and the frequency of development of anti-HLA antibodies were significantly reduced. Duration of hospitalization, readmission, infections, and malignancy were not different

Dose: Basiliximab 20 mg at induction followed by 20 mg on fourth postoperative day.

Intravenous Immunoglobulin

Intravenous immunoglobulin (IVIG) is comprised of 90% IgG, extracted from pooled plasma from between 50,000 and 100,000 blood donors. A number of immuno modulatory effects have been described for IVIG including blockade of Fc receptors, complement inhibition, and down regulation of B-lymphocyte receptors

IVIG is generally well tolerated with a <5% incidence of adverse reactions including mild infusion-related effects (usually first dose) that generally improve with temporary cessation or reduction in infusion rate, anaphylactic reactions associated with IgA sensitization in patients with IgA deficiency, thrombosis, and volume overload. The latter is due to an average volume requirement of 1 to 1.5 L (treatment dose 1-2 g/kg) and sodium load for drug administration, and poses difficulties for its application in patients with cardiac AMR with concurrent allograft dysfunction and heart failure.

Montgomery et al. reported superior patient survival for sensitized individuals undergoing desensitization with IVIG and plasmapheresis prior to transplant in comparison to patients undergoing an HLA-matched transplant [10].

IVIG has also been used successfully to treat AMR after heart transplant, usually in combination with plasmapheresis and rituximab. Data from large case series are, however, not available, and IVIG has not been systematically evaluated for the treatment of AMR after heart transplant. Jordan et al. were the first to describe the successful treatment of AMR after heart transplant with IVIG. Three cardiac and seven renal transplant patients with severe AMR were treated with IVIG. All cardiac patients had reversal of AMR and survived to six months. All seven renal patients recovered with no recurrent events. All ten patients demonstrated a rapid reduction in DSA.

Anti-CD20 antibodies:

Rituximab:

Rituximab (anti-CD20 monoclonal antibody) eliminates most B cells and Rituximab is used off-label in combination with maintenance immunosuppressive drugs, plasmapheresis, and intravenous immune globulin to suppress deleterious alloantibody responses in transplant recipients. Although plasma cells are usually CD20 negative, many are short-lived and require replacement from CD20-positive precursors. Thus, depletion of CD20-positive cells does reduce some antibody responses. CD20-positive B cells can act as secondary antigen-presenting cells, which raises the possibility that rituximab can ameliorate T-cell responses.

Off-label applications for rituximab include treatment of antibody-mediated rejection and possibly severe T-cell–mediated rejection and suppression of preformed alloantibody before transplantation. Again, controlled trials are needed.

Antibody-mediated rejection is a major cause of graft dysfunction. Although plasmapheresis is effective in removing alloantibodies (donor-specific antibodies) from the circulation, rebound synthesis of alloantibodies can occur.

Splenectomy is used in desensitization protocols for ABO-incompatible transplants and for antibody-mediated rejection refractory to conventional treatment. Also used are agents targeted for plasma cells, B cells, and the complement cascade, which are bortezomib, rituximab, and eculizumab, respectively.

Rituximab is a chimeric monoclonal IgG antibody, comprised of human constant regions and mouse variable regions directed against the CD20 pan-B lymphocyte surface molecule. Rituximab depletes B-lymphocytes by antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and induction of apoptosis through CD20 cellular cross linking and caspase activation.

The efficacy of Rituximab for AMR treatment after heart transplant has only been examined in case reports and one small case series (n = 8)[11]. The majority found a benefit by demonstrating improved allograft function. Most centers, however, administered rituximab in combination with other treatments, preventing sole evaluation of rituximab.

Although the ideal dosing for rituximab is unknown, a commonly used regimen in these and hematologic studies is 375 mg/m^2/week for up to 4 weeks. Pharmacodynamic studies in patients with lymphoma have shown maximal B-lymphocyte depleting effects at three to four months with low or undetectable numbers in the peripheral blood for up to six months and full recovery within 12 months [12].

The safety and tolerability of rituximab is well established in the context of hematologic malignancies. Mild-to-moderate first dose infusion-related reaction with fever and hives account for the majority of adverse effects. Concerns have, however, been raised over an increased risk of serious infections with rituximab therapy after transplantation. In a study of 22 renal transplant recipients, rituximab was shown to be effective in treating

AMR but associated with a high incidence of infection. Eighty-six percent of patients experienced serious infection including three cases of septic shock. It is probable that cumulative immunosuppression was intense and contributed to the development of infection as rituximab was administered in combination with six sessions of plasmapheresis, pulse steroids, tacrolimus, mycophenolate mofetil as well as cytolytic antibodies in a proportion of patients.

Antibody Mediated Rejection (AMR) is caused by antibodies directed against the donor organ and in heart transplantation can be both difficult to diagnose and treat. While graft dysfunction may be present in some cases, in others there is only pathologic evidence, or sometimes no other notable cause for graft dysfunction. Rituximab is a monoclonal antibody directed against CD20 and is utilized to suppress or deplete the circulating mature B-cells.

Dose: 375mg/m2 IV every week via high flow vein for a total of usually up to 4 weeks total

Bortezomib:

Proteasomes are responsible for the processing and degradation of ubiquitin-labeled proteins. Bortezomib is a selective 26S proteasome inhibitor depleting plasma cells and antibody production by inducing apoptosis via cell cycle arrest as well as inducing the unfolded protein response due to increased endoplasmic reticulum stress from accumulation of misfolded proteins. Additional immuno modulatory effects of bortezomib include gene transcriptional activator nuclear factor kappa B inhibition and inhibition of antigen processing by preventing peptide generation and MHC class I expression.

Bortezomib is currently approved for the treatment of multiple myeloma. Small studies in renal transplant patients have shown that bortezomib effectively decreases HLA antibodies in patients with stable renal function and is effective in treating refractory AMR .Woodle et al. recently presented results from the largest multicentre study of 107 cases of AMR in 91 solid organ transplant recipients[13]. The patient population comprised predominantly of kidney transplant recipients (n = 8 1), but also included five heart transplant recipients. Bortezomib was administered in four doses, each preceded by plasmapheresis, and all patients also received a single dose of rituximab. Over an average 9 month follow-up, 58% of patients showed histological improvement, with 81% and 96% graft and patient survival, respectively. Additionally, there was a >50% reduction in DSA in 40% of patients at 14 days after treatment. An 11.2% incidence of opportunistic infection was reported. Studies in transplantation and multiple myeloma series have reported high tolerability of Bortezomib with common adverse effects including fatigue, gastrointestinal toxicity, thrombocytopenia, neutropenia, and peripheral neuropathy.

Two cycles of bortezomib together with methylprednisolone, immunoadsorption, rituximab, and supplementary doses of intravenous immunoglobulin G reversed signs of heart failure, production of donor-specific antibodies, and findings of antibody-mediated rejection in biopsy. This treatment regimen was tolerated with only mild hematologic toxicity and proved to be successful during a 12-month follow-up[16]

Dose: Two cycles of Bortezomib -1.3 mg/m2 on days 1, 4, 8, and 11.

Eculizumab

Eculizumab is a humanized monoclonal antibody directed against C5, thereby preventing complement activation by inhibiting cleavage of C5 to C5a and C5b, and formation of the membrane attack complex. Eculizumab is currently approved in the United States for the treatment of paroxysmal nocturnal hemoglobinuria. At present, clinical studies of eculizumab in AMR are observational and preliminary. Locke et al. reported the successful treatment of a renal transplant recipient with refractory AMR using eculizumab[14]. In another study of highly sensitized renal transplant patients with DSA, a significant reduction in incidence of early AMR at <3 months was demonstrated for eculizumab option (6.25% incidence of AMR for eculizumab treated group compared to 40% for the historical control group) [15] in cases with severe AMR that are resistant to conventional therapy.

7. MONITORING AFTER HEART TRANSPLANTATION AND TREATMENT OF REJECTION:

Introduction:

It is an Established fact from the UNOS and ISHLT database that the long term survival of the graft after Heart Transplantation depends mainly on Immunological factors and the suppression of the hostile immune response mounted by the host. (1). Here it is pertinent to mention the main types of rejection OR HOST VERSUS GRAFT REACTION. They are (2):

A.Hyperacute rejection:

- Mediated by pre-existing IgM alloantibodies
- Antibodies come from carbohydrate antigens expressed by bacteria in intestinal flora against ABO blood group antigens

The antibodies act against vascular endothelium and create damage through complement activation.

Subsequent tissue necrosis Is through vascular thrombosis.

B.Acute Rejection:

– Occurs within days to 2 weeks after transplantation, 80-90% of cases occur within 1 month.

Pathology

– Acute humoral rejection
  - Acute vasculitis manifested mainly by endothelial cell damage
– Acute cellular rejection
  - Parenchymal cell necrosis along with infiltration of lymphocytes and macrophages

Mechanisms

– Vasculitis
  - IgG antibodies against alloantigens on endothelial cell
– Parenchymal cell damage
  - Delayed hypersensitivity mediated by CD4+Th1
  - Killing of graft cells by CD8+Tc

c. Chronic graft rejection:

Occurrence in time

– Develops months or years after acute rejection reactions have subsided

Pathology

– Fibrosis and vascular abnormalities with loss of graft function

d. Chronic allograft vasculopathy:

Mediated by chronic selective inflammatory damage to coronary Arteries, which leads to multifocal or diffuse fibrosis and stenotic lesions. Higher incidence of CAV is seen with CMV infection.

By Immunological types, the main three important mechanisms of rejection are:

a. CELL MEDIATED REJECTION : Mediated by CD 4 and CD 8 T-lymphocytes and macrophages
b. ANTIBODY MEDIATED REJECTION : Mediated by circulating allo-antibodies
c. MIXED REJECTION : Mediated by both mechanisms

1. Immunological matching before heart transplant using cadaver donor : The Immunological Matching prior to Heart Transplant in Indian practice Normally Involves the Following process:

- ABO Blood group Match
- Quantitative anti- HLA Pre formed antibodies or Panel reactive antibodies (PRA). Panel reactive antibody measurement is a preliminary test in which recipient serum is tested for percentage of positive antibody levels against a pre –determined panel of HLA antigens. Less than 10% PRA value is acceptable, if the value is 10-50% then a single antigen bead MFI should be done. The single antigen bead HLA antibody assay tests the exact antibody level to different HLA Class 1 or Class 2 antigens measured as per their MFA (Mean Flourescent Index) by Luminax technique or measure antibody levels using Flow cytometry. Very high level of PRA above 75 % or high levels of donor specific antibodies (more than 2000 MFI) would constitute a very high risk case for Heart Transplant and higher risk for both hyper acute rejection as well as higher risk for recurrent antibody mediated rejection and poorer one year outcomes after HTX (3,4). Such cases with high PRA's can be taken for heart transplant after desensitization protocols and if required pre or peri operative plasmapharesis.
- Complement dependent cytotoxic assay (CDC assay) between donor serum and recipient lymphocytes which is routinely done as soon as donor serum becomes available(5).
- Virtual Crossmatch: It is standard practice in USA and UK to collect donor serum in ACT vials (Temperature 0-4 degrees) and perform a HLA typing (for HLA class 1 and Class 2 antigens) as soon as the donor is ready for organ donation. This HLA profile is then uploaded in a nationwide internet database. This enables the recipient hospital to check donor specific antibodies in the recipient against these donor related antigens and also match against the recipient HLA profile. This Process is called a "Virtual Cross match ". High levels of donor specific antibodies against multiple HLA sites would constitute a relative contraindication for transplant. Then donor serum is stored in minus zero temperatures for future use (6). Virtual cross match thus is different from prospective cross match using both donor and recipient HLA typing, as done for live solid Organ transplants.

  In the Indian Context where donor serum is neither stored nor sent for HLA typing, there is always a small but not insignificant chance that many cases where PRA was low against the standard HLA panel, donor specific antibodies could have been present in recipient serum. Also later testing for donor specific antibodies (DSA's) becomes very important in case of suspicion of antibody mediated rejection.

2. Surveillance Endomyocardial (EM) biopsies :

Surveillance Endomyocardial (EM) biopsies are routinely advocated weekly till first month. Then two weekly till second month and then monthly in the first year after heart Transplant in the United States i.e. a total of 13-16 Biopsies in the First year (7).The Idea is to diagnose any pathological rejection processes early enough to prevent clinical graft dysfunction.

Since Cost of EM biopsies is prohibitively high in India and recalling patients from far flung areas is difficult, it is was thought prudent to limit the number of EM Biopsies . This policy does not see to impact survival or rejection rates. In a series of 164 cases from India, clinical and biopsy proved rejection rates have remained very low (only 8 clinical or biopsy proved rejection in 164 in a 3 year period(8).

We recommend the first biopsy to be done before discharge at 2-4 weeks after the heart transplant, second biopsy within one month, then at three, six and twelve months. This is useful for monitoring and also for reducing immune suppression. After one year, endomyocardial biopsy is

recommended every year and coronary angiogram at one year and then every two years and earlier if required as per the clinical status of patient.

Extra care must be taken during the EM biopsy to make the procedure low risk by adopting all precautions like using a 6 F Mullins Sheath to introduce the 5 F bioptome and using ECHO guidance to place the sheath oriented towards the septum. In the 130 EM Biopsy procedures done, there were no cases of pericardial tamponade and only 2 cases of increased or new tricuspid regurgitation. The EM biopsy samples are sent for both cell mediate rejection (CMR) analysis and antibody Mediated rejection (AMR) analysis.

GRADES OF CMR (ISHLT GRADING) (9) :

- 0R Nil findings
- 1R sparse mononuclear infiltrate with up to one focus of myolysis
- 2R two or more sites of mononuclear infiltrate with focal myolysis
- 3R Diffuse MN infiltrates with multifocal myolysis ,oedema plus hemorrhage

GRADES OF AMR (ISHLT GRADING) (10):

- pAMR 1h – Vascular macrophage adherence – CD 68 staining
- pAMR 1i – Linear C4d Staining around blood vessels
- PAMR 2 – Both above
- pAMR3 – Above Plus fibrin deposits plus polymorph leucocytes plus HLA DR2

and features of myocardial necrosis or cell damage

3. Non biopsy surveillance tests for Heart transplant rejection :

1. ALLOMAP test :

- The AlloMap test is a 20-gene, real-time, quantitative polymerase chain reaction (qRT-PCR) assay. AlloMap testing applies a proprietary mathematical algorithm that combines the gene expression values from genes associated with cardiac allograft rejection and generates a single clinically actionable score. Results are reported as an AlloMap score - an integer ranging from 0 to 40.
- AlloMap testing is indicated for use in detecting the absence of acute cellular rejection (ACR) in clinically stable cardiac transplant patients who are:
- ≥15 years of age
- >2 months post-transplant

UTILITY VALUE:

- Longitudinal non-invasive surveillance for ACR
- Monitoring for ACR while modifying immunosuppressant regimen
- Identify patients early post-transplant who belong to a very low risk group for ACR within the next few months
- Alternative to biopsy in patients with access problems
- Provide additional information in the management of patients with “mild rejection” of biopsy or unclear clinical presentation

ALLOMAP test has a better negative predictive value as shown in the CARGO – Trial (2006) in 63 asymptomatic patients an ALLOMAP –score of less than 30 –correlated with a negative predictive value of 99.6 % for rejection episodes more than 1 yr after heart transplant . (11)

2. Donor derived Cell free DNA:

Application of this assay to clinical samples from heart transplant recipients in a few studies demonstrated increased levels of Dd-cfDNA in patients with biopsy-confirmed rejection and decreased levels of dd-cfDNA after successful rejection treatment.

The test involves use of NGS ASSAY for 266 SNP's and identifying statistical quantity of the donor cell free DNA in the recipient blood. The final clinical utility of this test as a standard for early diagnosis of rejection still remains to be validated. (12)

3. Donor specific antibodies :

Measurement of Donor specific anti HLA antibodies using the Single antigen Bead (SAB) method has been found useful for initial virtual cross match (once the donor HLA typing is done) and later to assess antibody levels during or after a rejection episode .

These antibodies are classified as:

MHC CLASS 1 Antigens --- HLA –A, HLA B and HLA C

MHC CLASS 2 antigens –HLA DP, DQ, DR.

The antibodies are measured commonly using Luminax method using Ssngle antigen columns and the results expressed as "Mean fluorescent Index "(MFI) (13). Value of donor antibodies to monitor rejection has been found to be especially useful in peadatric heart transplant recipients.

4. Prevention of rejection using optimal drug dosage and serum levels**:** The cornerstone of rejection avoidance is administering immunosuppressent drugs at optimal dosages as dictated by blood levels. The recommended trough (C0) levels for common immunosuppressent drugs in adult patients are :(14)

A. Tacrolimus :
   Early Post operative period up to 60 days = 8 -12 ng/ml
   3-6 months – 7 -10 ng/ml
   After 6 months – 5-10 ng /ml
B. Everolimus : 3-8 ng/ml
C. Mycophenolate : 1.9 – 4 mg/ L
D. Cyclosporine :
   First 3 months: 275-375 ng/ml
   After 3 months: 100-150 ng/ml

<u>TREATMENT OF REJECTION:</u>

1. Cell mediated rejection : (15)

It has been pointed out by experts that there can be occasional disparity between the Grade of CMR as seen on EM biopsy and actual clinical status of patient. Following are the current ISHLT suggested approaches to a case with cell mediated rejection as detected by surveillance EM biopsy:

A. Asymptomatic Grade 1 R: No extra therapy needed. Surveillance EM biopsy as per protocol.
B. Asymptomatic Grade 2 R: either IV corticosteroids or extra dose of oral steroids as per other findings like ECHO based LV or RV function.
C. Asymptomatic Grade 3 R: IV pulse steroids advised (dose 1000 mg per day for 3 days). This to be followed by daily ECHO monitoring of ventricular function and EM biopsy after 1-2 weeks. Immunosuppression drugs like tacrolimus and Mycophenolate should be up titrated.

D. Symptomatic grade 2 R or 3 R rejection: IV pulse steroid as per above protocol. Close Echo follow-up. Up titration of Immunosuppression drugs. Inotropes for any ventricular dysfunction or haemodynamic compromise. In addition for patients with incomplete response or haemodynamic compromise, IV anti thymocyte globulin daily dose for 7-10 days is strongly recommended.
E. Recurrent or resistant rejection: Needs additional course of polyclonal anti thymocyte globulin, photopheresis twice weekly or pulse therapy with methotrexate (2.5-20 mg weekly – for three to four weeks) can be considered.
F. IL -2 receptor blockers like basiliximab not indicated for treatment of acute cellular rejection.
G. In a patient with low grade CMR by EM biopsy and hemodynamic compromise or ventricular dysfunction the possibility of antibody mediated rejection should be considered.
H. In cases of asymptomatic grade 2 R rejection findings after 1 year of heart transplant – No treatment is generally necessary and close follow-up advised with follow-up EM biopsy.
I. All cases- Intravenous antibiotics as prophylaxis for opportunistic infections advised

Of course the Incidence of CMR is highest in the first few weeks after heart transplant and becomes rare after 3 months.

1. Antibody Mediated rejection : (15)

Following are the ISHLT recommendations for acute antibody mediated rejection:

1. Acute antibody mediated rejection with haemodynamic compromise or heart failure: First Pulse Corticosteroid with IV solumedrol 1000 mg per day for 3 days. Then Plasmapharesis 1-2 Plasma exchanges per day for 3-5 days advised. IV immunoglobulin 1000 mg/kg, 1-3 times per week for 1-2 weeks recommended. Additionally followed by IV Rituximab 375 mg / m2 weekly doses for 3 weeks recommended for severe or recurrent cases. Intravenous inotropes or IABP or MCS to be used for stabilization of the haemodynamic status.
2. Maintenance Therapy after an acute episode: Increase in tacrolimus levels, addition of Everolimus to be strongly considered. Follow-up EM biopsies mandatory after 1-2 weeks to be repeated if necessary.
3. Many centres now use Donor specific antibodies (DSA) as additional test to monitor recovery for an acute Antibody, mediated rejection episode apart from Non EM biopsy measures like ALLOMAP and DS cell free DNA monitoring.
4. Acute Antibody rejection with ventricular dysfunction and Mild failure should also be treated aggressively in above Lines, because the condition often progresses in an unpredictable fashion and can recur within days.
5. Asymptomatic Antibody Rejection: There is evidence that such cases may progress to chronic allograft vasculopathy and recurrent rejection. Hence up titration of immunosuppressives and addition of mTOR Inhibitor like Everolimus is strongly recommended. Follow-up with DSA or ALLOMAP recommended by some centres.
6. Paedatric Heart Transplant cases: Many children are highly sensitized in the pre operative period due to prior cardiac surgery or blood Transfusions. Also children with antibody rejection are likely to be sicker for same grade of AMR and hence need early institution of inotropes. Pulse steroids and plasmapharesis are indicated early .In severe or refractory cases, anti thymocyte globulin are indicated. Grade 1 rejection with more diffuse Infiltrates need up titration of Immunosuppression drugs.
7. Resistant or refractory AMR: Photopharesis, splenectomy and anti lymphocyte globulin have been considered by many centres for AMR.

Although the advent of immunosuppressants, such as Tacrolimus, has significantly lowered the frequency of acute cellular rejection after heart transplantation, the incidence of AMR remains relatively unaffected. The problem of AMR remains unsolved because standardized schemes for diagnosis and treatment remain

contentious, and current immunosuppressive regimens are largely intended to interfere in T-cell signaling pathways.

As a result, AMR continues to appear in roughly 10% to 20% of heart transplant patients, correlating with factors of poor outcome such as increased incidence for hemodynamic compromise rejection, greater development of cardiac allograft vasculopathy (CAV), and higher incidence of death.

A number of studies have examined the many different features of AMR. From these mainly observational studies, AMR has been found to occur both early and late after transplantation and has been identified with risk factors such as female gender, elevated pre-transplant panel-reactive antibodies (PRAs), development of de novo DSAs late after transplantation, positive donor-specific crossmatch, prior sensitization to OKT3, cytomegalovirus (CMV) seropositivity, prior implantation of a ventricular assist device, and retransplantation. (16)

Anti –HLA antibodies and Anti body mediated rejection (AMR)

The development of anti-HLA antibodies after transplantation has been implicated in allograft injury. Tambur et al demonstrated that de novo production of antibodies during the first year after transplantation is significantly associated with cellular rejection and that class II antibodies significantly correlate with mortality and cardiac allograft vasculopathy (CAV). Post transplantation panel reactive anti-HLA antibodies (PRAs) are associated with the development, frequency, and severity of CAV. Early and persistent anti-HLA antibody is associated with worse survival and CAV. DSAs, on the other hand, are associated with cellular rejection, AMR, and increased incidence of CAV. (17)

The improved detection of anti-HLA antibodies has thus enabled the use of a virtual crossmatch in performing heart transplantation- Conceivably, the use of virtual cross-match for transplantation in a patient with circulating anti-HLA antibodies, using a donor without unacceptable HLA antigens could prevent DSA-mediated AMR. The development of AMR could also be attenuated by identifying the high-risk patient in the immediate pre-operative or post-operative period by performing flow cytometry-based crossmatch, a technique that is more sensitive than complement-dependent lymphocytotoxicity techniques. A positive flow cytometry-based crossmatch has been associated with subsequent development of AMR and reduced survival. (18)

8. INDICATIONS FOR LUNG & HEART-LUNG TRANSPLANTATION:

Lung transplantation is now an accepted therapy for the management of a wide range of end stage lung diseases. There is clearly a survival benefit for lung transplant recipients along with improvement in quality of life. This document is in line with the consensus opinions published by ISHLT in 3 editions regarding the Selection of Lung Transplant Candidates (1998,2006 and updated consensus opinion in 2014) [1,2,3]. Lung transplantation should be offered and the patient should be actively listed when life expectancy after transplantation exceeds life expectancy without the procedure.

Lung transplantation Indications:

Lung transplantation is indicated for patients with chronic, end-stage lung disease who are failing maximal medical therapy, or for whom no effective medical therapy exists. The goal of lung transplantation is to provide a survival benefit, along with improvement in quality of life. Lung transplantation confers significant survival benefit, particularly in patients with advanced cystic fibrosis, idiopathic pulmonary fibrosis, and primary pulmonary hypertension [4, 5, and 6]. The patients with COPD and Eisenmenger's syndrome may not have survival benefit but they clearly have quality of life improvement with lung transplantation [7]. Lung transplantation for most patients is a palliative rather than curative treatment, and improvements in quality of life in addition to survival should be used to assess the effectiveness of the procedure [8]. Lung transplantation should be offered to adults with an array of end stage respiratory disease wherein -

1. There is more than 50% risk of death from lung disease within 2 years.
2. More than 80% likelihood of surviving at least 3 months post lung transplantation.
3. More than 80% likelihood of 5-year post-transplant survival from a general medical perspective.

Lung transplantation can be offered to four broad groups of etiologies-

1. Obstructive lung disease: COPD, alpha-1 antitrypsin deficiency emphysema, obliterative bronchiolitis.
2. Interstitial lung disease: Idiopathic pulmonary fibrosis and other causes such as sarcoidosis, connective tissue diseases etc.
3. Suppurative lung disease: Cystic fibrosis, bronchiectasis.
4. Vascular disease: Pulmonary hypertension, Eisenmenger syndrome.

COPD (34%), IPF (23%) and cystic fibrosis (16%) form the largest groups that undergo lung transplantation. (ISHLT 2012 data)

The situation in India is little different. Most of the referrals for lung transplantation are the patients with IPF. COPD constitutes a negligible subgroup referred for transplantation (as opposed to the western data).

Pulmonary fibrosis

The median survival for idiopathic pulmonary fibrosis from the time of diagnosis is only 2.5–3.5 years. Idiopathic pulmonary fibrosis which is synonymous with usual interstitial pneumonia (UIP) is the most common and most serious of the idiopathic interstitial pneumonias (IIPs) .It has the highest mortality rate in patients waiting for lung transplantation. Therefore, timing of referral and listing is paramount to provide them with best chance of survival. Some earlier investigators showed an increased mortality in patients with IPF with a forced vital capacity (FVC) of less than 60% predicted. More recent data from a large cohort suggests that patients with relatively well preserved lung volumes are at similar risk of mortality, as are those patients with lower levels of lung function. TLCO has been identified as the most reliable marker of deterioration in IPF and an absolute value of <39% predicted indicates the highest mortality risk. (9) In patients with non-specific interstitial pneumonia (NSIP), a DLCO of <35% predicted, is associated with high mortality. A drop in vital capacity (VC) of >10% in 6 months and oxygen saturations on air <88% during a 6-min walk test are other indicators of poor outcome and should prompt immediate referral for transplantation.(10)The rate of disease progression rather than an absolute cut off in lung function which should guide referral and listing . High-resolution computed tomography (HRCT) displaying honeycombing in patients with usual interstitial pneumonia has a higher mortality than those without these typical features and should guide early referral.

In summary, physicians should consider specialist referral for lung transplantation in case of evidence of usual interstitial pneumonitis (UIP) or fibrosing non-specific interstitial pneumonitis (NSIP) in association with any of the following

1) FVC less than 80% predicted or DLCO less than 40% predicted.
2) Any dyspnea or functional limitation attributable to lung disease.
3) Any oxygen requirement.

A patient with IPF should be listed actively for lung transplantation if there is a histological or radiographic evidence of UIP associated with:

1) A 10% or greater fall in FVC in last 6 months.
2) A DLCO of less than 39% predicted or decline of more than 15% in 6 months.
3) Fall in oxygen saturation below 88% during a 6-MWT or distance less than 250 m on 6-minutewalk test or 50 m decline in 6-minute-walk distance over a 6-month period.
4) Honeycombing on HRCT.
5) PAH in RHC or Echocardiogram.
6) Hospitalization due to acute exacerbation.

COPD

The decision regarding correct timing for transplantation may be difficult in the COPD patients because patients with COPD may have relatively good prognosis despite severe symptoms. In India, the referral for transplantation

for patients with COPD is quite low. The reasons could be advanced age of COPD patients and perceived notion of reasonable survival even in oxygen dependent patients, despite poor quality of life.
Acute exacerbation and hospital admission associated with hypercapnia carries a poor prognosis, with a 49% 2-year survival [(11)] and hence should have prompt referral for transplantation.
In the context of COPD, BODE index has been found to be a good guide for transplant referral [(12)]. BODE index is calculated with the BMI, the degree of airflow obstruction (FEV1), dyspnea (MMRC dyspnea scale), and the exercise capacity (assessed by the 6-minute walk distance). BODE index of 7 to 10 (on a scale from 0 to 10) was associated with a median survival of about 3 years ,which is less than would be expected after transplantation. Patients with a BODE score of 5 to 6 would likely not derive a survival benefit from transplantation but may be candidates for early referral.
Patients with an FEV1 of less than 20% and either a DLCO of less than 20% or homogeneously distributed emphysema also have a high mortality with a median survival of about 3 years with medical therapy [(13)].

Timing of referral:

1) Progressive disease, despite maximal treatment.
2) Disease is advanced where patient is not a candidate for endoscopic or surgical lung volume reduction surgery(LVRS.)
3) BODE index of 5 to 6.
4) PaCO2 more than 50 mm Hg or PaO2 less than 60 mm Hg
5) FEV1 less than 25% predicted.

In summary, a patient with COPD should be actively listed for lung transplantation

1) Patients with a BODE index of 7 to 10 or at least 1 of the following:
2) Acute exacerbation with hypercapnia.
3) Three or more severe exacerbations during the preceding year.
4) Patients with PAH.
5) FEV1 of less than 20%
6) DLCO of less than 20%.

Cystic Fibrosis and Other Causes of Bronchiectasis:
CF patients are chronically infected with drug resistant organisms that colonise the upper respiratory tract and sinuses. In the setting of severe immunosuppression post transplantation, this can lead to allograft infection and sepsis. CF also has multisystem involvement that poses extra challenges to identify a suitable candidate for transplantation.
Colonization with organisms such as *Pseudomonas,* Klebsiella, *Stenotrophomonas, methicillin resistant Staphylococcus aureus (MRSA)* and Aspergillus *fumigatus* are not contraindications to transplant but require careful planning and antibacterial regime. Colonization with *Mycobacterium abscessus* or *Burkholderia cenocepacia* are considered as contraindication for transplantation in most of the centers due to the very high risk of sepsis post-transplant with these pan resistant bacteria.
Antimicrobial sensitivity testing should be done at regular intervals while awaiting a transplantation to ensure that antibiotic combination at the time of transplant is effective.
In practice, transplantation for a patient with CF should be discussed with the patient and family when FEV1 decreases to about 30% of predicted, or when there is a rapid decline in FEV1[(15)] . Early referral is recommended in female patients younger than 20 years as they deteriorate rapidly and have a particularly poor prognosis. Any hospitalization requiring ICU treatment for a pulmonary exacerbation also deserves prompt referral for transplantation. A 6-minute walk distance less than 400 m and pulmonary hypertension have been associated with a poorer prognosis [(16)].

In summary, a patient with CF should be referred for lung transplantation

1) Increasing frequency of exacerbations requiring antibiotic therapy and hospitalizations
2) FEV1 below 30% predicted or a rapid decline in FEV1
3) Clinical deterioration in young female patients.

4) Refractory and/or recurrent pneumothorax.
5) Recurrent hemoptysis not controlled by embolization.
6) A 6-minute walk distance less than 400 m.
7) PAH in the absence of a hypoxic exacerbation

Patients with CF should be listed for transplantation in case of oxygen-dependent respiratory failure.

Timing of active listing for transplantation:
1) Hypoxia with PaO2 less than 60 mm Hg.
2) Hypercapnia with PaCO2 more than 50 mm Hg
3) Pulmonary hypertension.
4) Frequent hospitalization.
5) Rapid lung function decline.

Pulmonary Arterial Hypertension

It's crucial to differentiate the PAH according to its cause, as the prognosis differs amongst the groups. The prognosis for PAH due to congenital shunts, IPAH, systemic sclerosis, veno-occlusive disease and pulmonary hemangiomatosis fares from fair to worse in that order.

Idiopathic PAH (IPAH) has a median survival rate of 2.8 years when untreated [(17)]. Over the past decade, there has been significant improvement in the prognosis on account of advances in medical therapy for PAH [(18)]. Prostacyclin analogs are often a key part of the treatment regimen. In the USA and Europe, options include intravenous epoprostenol, inhaled iloprost, and treprostinil. As a result fewer PAH patients are being referred for lung transplantation. PAH due to congenital left-to-right shunt have better prognosis than IPAH while awaiting transplantation.

IPAH with NYHA iii or IV symptoms or a 6 minute walk distance less than 332 meters has been shown to have poor survival and should prompt immediate referral [(19).]

Other indications for referral include right heart catheterization showing right atrial pressures of more than 15 mmHg or a cardiac index of less than 2 L·min−1·m−2 together with intractable right heart failure despite being on maximal medical therapy . Patients now referred are frequently those failing on maximal medical treatment with a highest tolerated dose of intravenous prostaglandin therapy in association with one or two other targeted therapies including phosphodiesterase-5 inhibitors and endothelin receptor antagonists.

In summary, a patient with PAH should be referred for lung transplantation -

1) NYHA Functional Class III or IV symptoms during escalating therapy.
2) Worsening disease.
3) Use of IV prostacyclin.
4) Pulmonary veno-occlusive disease (PVOD) or pulmonary capillary hemangiomatosis.

Patients with PAH should be listed and offered lung transplantation when-

1) Persistent NYHA class III or IV on maximal medical therapy.
2) Right heart catheterization showing cardiac index of less than 2 liters/min/m2 and right atrial pressure more than 15 mm Hg.
3) Less than 350 meter of 6-MWT.
4) Intractable right heart failure despite intravenous epoprostenol, or equivalent.

Sarcoidosis:

Sarcoidosis is an indication for 2-3% of the total adult lung transplants. Although it's not as common an indication for lung transplant as idiopathic pulmonary fibrosis, pulmonary Sarcoidosis carries a similar or higher (up to 50%) mortality in patients on the waiting list. The concomitant extra pulmonary, such as cardiac, hepatic or neuro involvement complicates the decision to refer for transplantation. Some of these patients have significant bronchiectasis with bacterial colonization and aspergillomas that portend poor prognosis.

Triggers for referral should include NYHA class III/IV symptoms, hypoxia at rest and significant secondary pulmonary hypertension.

In summary, a patient with Sarcoidosis should be referred for lung transplantation

1) NYHA functional class III or IV symptoms and any of the following:
2) Rest Hypoxia.
3) Significant secondary pulmonary hypertension.
4) Right atrial pressure more than 15 mm Hg.

Lung carcinoma (Bronchoalveolar carcinoma)

Compared with the natural history of diffuse and bilateral BAC and the ineffectiveness of chemotherapy, survival after lung transplantation is far superior to that of the natural history of the disease, despite high recurrence rates of BAC after lung transplantation.
Prior to the referral for lung transplantation, the histopathology should be done to rule out more invasive forms. Detailed staging of the disease should be done with bone x-rays, whole body CT, brain magnetic resonance imaging, bone scans, and positron emission tomography. These tests should be repeated regularly (every 3 months is suggested) to detect metastases. In the presence of disease extension beyond the lungs, patient should be delisted.
ISHLT reports survival of 53% at 5 years and 31% at 10 years reported by the ISHT in the 2013 Registry report [20]. Many of these patients (59%) developed a recurrence of BAC 5 to 49 months after transplantation but despite recurrence, the overall survival was better than the expected survival without transplantation.

Conclusion:
With improved methods of diagnosis and effective management of chronic respiratory diseases in India, the number of patients with end-stage respiratory disease who may require lung transplantation for survival and/or long term quality of life is likely to increase. It is beneficial to discuss individual cases with the local lung transplant centre in the event of any uncertainty about the suitability of a patient. The guidelines discussed are formed from expert consensus opinion as there is little evidence and often no randomized controlled trials to support the recommendations.

Combined Heart-lung transplantation:

Indications:

Combined heart and lung transplantation is limited to patients in whom it offers the only surgical option for their end-stage cardiac and pulmonary disease. The perceived superiority of double lung transplantation has markedly reduced the need for the combined heart-lung procedure (40 percent decrease in the number of centers performing heart-lung transplants since 1994) [21]. The decline is also attributable to the new medical therapies for patients with pulmonary arterial hypertension and congenital heart disease with Eisenmenger syndrome.
With current evidence, isolated lung or heart transplantation is preferred to heart-lung transplantation because of few significant disadvantages with the combined procedure.

1) A heart–lung block is difficult to obtain and can lead to increased waiting time and increased mortality among patients awaiting combined heart-lung transplantation compared with those waiting for isolated heart or lung transplants.
2) A combined procedure exposes the recipient to risks of both graft coronary artery vasculopathy and BOS (bronchiolitis obliterans syndrome).
3) heart-lung recipients may be disadvantaged by the compulsory requirement for cardiopulmonary bypass during surgery and the physiological effects of a denervated heart.
4) The ISHLT registry data shows survival rates of 71% at 3 months, 63% at 1 year, 44% at 5 years and 31% at 10 years, which clearly are inferior to the outcomes with lung transplantation alone.

Major indications for a combined heart lung transplant can be summed as following:

-Congenital heart disease with Eisenmenger syndrome — 36.5 percent
-Idiopathic pulmonary arterial hypertension — 27.5 percent. Previously, idiopathic pulmonary hypertension was the most common indication. However, it has been shown that right ventricular failure can be reversed after double lung transplantation. Therefore, patients with idiopathic pulmonary arterial hypertension (IPAH) should not undergo combined heart-lung transplantation unless left ventricular dysfunction co-exists. However, further study is necessary to determine whether double lung transplant is sufficient even for patients with inotropic dependency for right ventricular failure.
-Cystic fibrosis — 14.0 percent
-Acquired heart dysfunction with PAH -5%.Pulmonary hypertension with irreversible PVR ≥4 Wood units is commonly considered a contraindication to isolated heart transplantation and in this setting, heart-lung transplantation may be considered as an alternative
-COPD (emphysema) - 3.8%.
-Idiopathic pulmonary fibrosis- 3.1%.Heart-lung transplantation may also be required in patients with end-stage parenchymal lung disease who also have severely compromised left ventricular function (e.g., Sarcoidosis). In most patients with pulmonary arterial hypertension and preserved left ventricular function, there is no advantage to heart-lung transplantation compared with isolated bilateral lung transplantation, even in the presence of significant right ventricular dysfunction [22, 23, and 24].

Great disparity exists among centers in regard to the lowest acceptable right and left ventricular ejection fraction for bilateral lung transplantation (particularly among patients with idiopathic pulmonary arterial hypertension) and some centers prefer combined heart-lung transplantation if severe dysfunction exists. The cut-off values range from approximately 10 to 25 percent for right ventricular ejection fraction and 32 to 50 percent for left ventricular ejection fraction based on published reports; values below these thresholds may trigger consideration of heart-lung transplantation.

In nutshell

1. Irreversible primary pulmonary hypertension with heart failure;
2. Eisenmenger complex.
3. Pulmonary fibrosis, with severe left ventricular dysfunction.
4. Cystic fibrosis with severe heart failure;
5. Chronic obstructive pulmonary disease with heart failure;
6. Emphysema with severe heart failure;

9. IMMUNOSUPPRESSION AFTER LUNG AND HEART-LUNG TRANSPLANTATION

Over the last five decades, the experimental work in the field of immunosuppression transplantation has grown by leaps and bounds. In the current era, the excellent results achieved in thoracic organ transplantation is attributed to sophisticated immunosuppressive regimens. Currently, 'Triple drug immunosuppression' therapy is widely adopted in lung and heart and lung transplantation, that includes a calcineurin inhibitor, an antiproliferative agent and a corticosteroid.

1. Calcineurin inhibitors:

Calcineurin inhibitors (CNIs) include cyclosporine (CsA) and tacrolimus (TAC).Currently TAC is the most commonly used CNI.

A.Cylosporine was the first FDA approved (1983) calcineurin inhibitor incorporated for the immunosuppression in transplant recipients. It is a lipophilic compound that binds to intracellular cyclophilin in T lymphocytes, inhibiting the transcription of interleukin 2, thus decreasing the activation and proliferation of T lymphocytes. The original cyclosporine (Sandimmune) described was an oil based compound with a very variable and unpredictable bioavailability. To enhance its bioavailability, a modified formulation (Neoral) was launched and approved by the FDA in 1997.

They are available in capsules, oral solution, and intravenous formulations. Therapeutic drug levels could be monitored by their trough (C0) values, AUC calculations, or 2-hour post-dose (C2) levels. Most centers either follow-up with the Co or C2 levels. .Although, studies in heart and lung transplants inferred a better correlation of C2 levels in avoidance of cyclosporine related nephrotoxicity, over other parameters. The target trough levels range from 100-450 ng/mL, or C2 levels 800- 1,400 ng/mL Major adverse effects of cyclosporine include nephrotoxicity (acute and chronic), hypertension, hypercholesterolemia, electrolyte abnormalities (hyperkalemia, hypomagnesemia), neurotoxicity (posterior reversible encephalopathic syndrome, seizures, headache, tremor), diabetes, hirsutism, and gingival hyperplasia.

B. Tacrolimus (previously known as FK506) (Prograf) was in use since 1997. It is known to be 10-100 times more potent than cyclosporine. Tacrolimus forms a complex with the intracellular FKBP12 and prevents the transcription of cytokines, (including interleukin 2), that in turn reduces the activation of T lymphocytes, similar to Cyclosporine.

Tacrolimus and Cyclosporine share many characteristics in common. Like cyclosporine, tacrolimus has poor and variable absorption, (17-23%). Both these drugs are metabolized by the hepatic cytochrome (CYP) P450 3A4 and 3A5 enzymes and p glycoprotein efflux pumps present on intestinal mucosa. They are prone to have significant drug interactions with CYP inducers (e.g., rifampin, phenobarbital, carbamazepine, and phenytoin) and inhibitors (e.g., azoles, macrolides, and calcium channel blockers). Additional drug interactions exist for cyclosporine, as it is not only a substrate of CYP 3A4 but also a moderate inhibitor (statins).

The target trough concentration is the most adopted parameter for therapeutic drug monitoring in the recipients (range 5-15 ng/mL). Both these drugs cause calcineurin inhibitor induced vascular constriction leading to hypertension but Tacrolimus, with perhaps less hypertension and hypercholesterolemia, and more neurotoxicity.

Apart from this, higher incidence of new onset diabetes has been reported with use of tacrolimus. Thrombotic thrombocytopenia purpura and hemolytic uremic syndrome were reported with both cyclosporine and tacrolimus. The vascular effect is also known to promote renal ischemia leading to renal tubular necrosis in acute setting. In view of its nephrotoxic effect, a newer once-daily extended-release formulation of tacrolimus was introduced (Astragraf XL) and was approved by the FDA in 2013, although no studies have been performed in heart and lung transplant recipients yet.

According to the most recent ISHLT Registry report, tacrolimus was the most frequently used calcineurin inhibitor, 83% at one year post-transplant, and 77% at 5 years post-transplant.

2. Anti-proliferative agents:

These are the antimetabolites that inhibit cellular proliferation by interfering with the denovo purine synthesis of the cell and S-G2 cell cycle arrest as well. The action is directed on both T and B lymphocytes.

A. Azathioprine was the first anti-proliferative agent introduced. It is converted to 6-mercaptopurine (6-MP) in vivo which then is converted into several compounds that get incorporated into the DNA of replicating cells , in turn inhibiting the proliferation. Azathioprine is associated with bone marrow suppression and gastrointestinal intolerance, apart from the hepatotoxicity (transaminitis and cholestasis) and pancreatitis in rare cases. Since the action of Azathioprine is dependent on its conversion by xanthine oxidase, patients receiving allopurinol and febuxostat (xanthine oxidase inhibitors) are prone to develop toxic side effects. Hence, a 75% of its dose reduction is generally recommended.

B. After the introduction of Mycophenolate mofetil (MMF), the use of azathioprine as an immunosuppressant has declined. MMF is an inhibitor of inosine monophosphate dehydrogenase, which is the rate-limiting enzyme of guanine nucleotide synthesis critical for de novo purine synthesis.

Doses range from 1-1.5 g IV or oral twice daily. It has got similar gastrointestinal and hematopoietic side effects as in azathioprine. Studies has shown better efficacy of MMF in the prevention of rejection compared with azathioprine. Earlier MMF was used as a rescue therapy in lung transplant recipients following the development of bronchiolitis obliterans syndrome, and improvement was noticed after switching from azathioprine. MMF is known to have teratogenic effects and hence, in case of pregnancy and lactation, azathioprine could be the preferred one.

C. Sirolimus and Everolimus are the two newer antiproliferatives. Both bind to intracellular

FK506 binding protein like tacrolimus. However unlike tacrolimus the complexes they form do not inhibit calcineurin but instead bind to mTOR, which is a signaling pathway needed to promote progression of the cell cycle

from G1 to S phase. Sirolimus is available as oral tablets and an oral solution. Doses range from 0.5-6 mg/day with target trough values ranging 5-15 ng/mL. Everolimus is available as oral tablets. Doses range from 0.25-3 mg twice daily, with target trough values ranging 5-15 ng/mL. The usage of mTOR inhibitors is identified in cases of calcineurin induced kidney dysfunction, supplementation along with the reduction in the dosage of calcineurin inhibitor has shown to improve the kidney function in such cases.

Despite a lack of definitive long term outcomes of the graft, MMF is used as the primary ant proliferative agent and is considered to have a better tolerability over mTOR inhibitors.

3. Corticosteroids:

Steroids have been the standard component of the immunosuppressant therapy in both induction as well as maintenance regimens. The commonly used ones are methyl prednisolone and prednisone. Their anti-inflammatory properties involve inhibition of the NFkB pathway, prevention of T cell proliferation, decreased macrophage activation, and inhibition of cytokine production. The recent ISHLT registry reported the usage of corticosteroids by almost all transplant centers, at one and five years post transplant.

The initial doses range from 500-1,000 mg given intraoperatively at the time of induction, followed by 250mg IV on day 1, 40 mg iv thrice a day on day 2 and switched to oral prednisone 1mg/kg/d on day 3. It is gradually tapered to 10mg/day in the first 3 months and then 5-7.5 mg per day for maintenance since then.

Despite several adverse effects associated with the use of corticosteroids (hypertension, weight gain, hyperlipidemia, hyperglycemia and diabetes mellitus, osteoporosis and increased risk of fractures, increased risk of cataracts, poor wound healing) , steroid abstinence is not encouraged in order to prevent allograft failure, instead is preferred to continue at the lowest possible dose.

4. Induction Therapy:

Few centers believe in supplementing a course of cytolytic drugs for 3 days or 10days, starting preoperatively to reduce the risk of acute cell mediated rejection. The primary target is T lymphocytes. Induction therapy serves to be beneficial in situations of compromised kidney function or hemodynamic instability, where there is a delay in initiation of calcineurin inhibitors.

A. Daclizumab and Basiliximab are the monoclonal antibody agents popular as induction therapy. Daclizumab is the humanized (90% human, 10% murine) monoclonal antibody removed from the US market by the FDA in 2009. Since then, Basiliximab (chimeric monoclonal antibody - 75% human, 25% murine), is the only IL2 receptor antagonist available for use. It is followed by a 2-dose regimen receiving intraoperatively and on day 4. It has a long half life of 10-14 days.

B. Anti thymocyte globulin (ATG) is the second most commonly used induction agent, used by roughly 20% of centers that utilize induction. ATG is a polyclonal antibody preparation isolated from either rabbit or horse sera which contains antibodies towards human thymocytes. The one other alternative for induction therapy is Alemtuzumab, a humanized (90% human 10% murine) monoclonal antibody against CD52. Most patients are prone to develop adverse effects with these agents like fever, chills, rash, arthralgia, diarrhoea, leukopenia, and thrombocytopenia, collectively known as 'cytokine release syndrome'. Pre-medication with acetaminophen, anti-histamines, and corticosteroids is advised to help minimize these reactions.

C. A Cochrane review inferred lower rates of acute rejection with induction therapy by IL2 receptor antagonists versus no induction therapy. However long term prospective studies are needed to determine the survival benefit of basiliximab.

4. Supportive Drugs :

In an attempt of protecting the transplant recipients from allograft rejection, they are at higher risk for developing infections. Hence, a universal prophylaxis is introduced in the peri and postoperative periods along

with the immunosuppressant multidrug regimen. A combination of antimicrobial, antiviral and antifungal drugs are included.

Trimethoprim-sulfamethoxazole (TMP-SMX) is supplemented as the antibacterial component, given universally to all transplant recipients who do not have sulfa allergies. TMP-SMX is effective for the prevention of *Pneumocystis* pneumonia (PCP), which has an incidence of 10 to 14% post transplant. It is also effective in giving protection against other pathogens, including Listeria monocytogenes *and* Toxoplasma gondii. It is given for 12 months post transplant. India, being a country with a higher prevalence of tuberculosis, Isoniazid also being used as a part of prophylaxis for 9 months.

The fungal infections in transplant recipients are high. Most fungal infections occur shortly after the transplantation during maximum immunosuppression and are caused by *Candida* or *Aspergillus* species. Fluconazole 400 mg/day for 10 weeks or liposomal amphotericin B 1 mg/kg/day for 5 days significantly reduced the incidence of invasive fungal infections. In patients with a history of previous fungal infection, secondary prophylaxis may be required.

Cytomegalovirus infection is a frequent complication after transplantation, seen 30-90days post transplant. The occurrence may be due to transmission from the transplanted organ, reactivation of latent infection, or after a primary infection in seronegative patients. The drug used is intravenous or oral ganciclovir, oral valganciclovir or less frequently, valacyclovir. Prophylaxis is continued for 3-6 months post transplant.

6. Conclusion:

There are many unanswered and important questions about immunosuppression. To quote Costanzia [(1)], these include whether new agents provide more specific or simply more potent immunosuppression, which combination of drugs can achieve maximal efficacy with minimal adverse effects, and whether the new agents will prevent chronic rejection and improve long-term survival.

The hope for the future is that specific inhibition of antigen recognition, T cell co-stimulation, and function of accessory molecules will induce long-term acceptance of a transplanted organ without the complications of 'broad spectrum' immunosuppression.

The immunosuppression after lung transplant is the balance between the exposure to a variety of infectious organisms and accompanying donor human leukocyte antigens.

10. MONITORING AFTER LUNG TRANSPLANTATION AND TREATMENT OF REJECTION

The process of transplantation mandates lifelong surveillance for health maintenance. After recovering from the lung transplant surgery, the recipients are at a risk for host of complications due to drug toxicity, immune suppression, rejection and infection. Put together they can contribute to significant morbidity, mortality and also adversely affect the long term outcome of the graft. In addition to the maintenance of lung allograft function, post-transplant surveillance helps in diagnosing and managing a diverse array of these medical complications and infectious diseases related to transplantation. Timely identification and proper intervention can avoid adverse outcomes associated with these complications.

1, Drug toxicity and medical complication of lung transplant

- Acute kidney injury
- Chronic kidney disease

- Coronary artery disease
- Hypertension
- Hyperlipidemia
- Obesity
- Diabetes mellitus
- Hyperkalemia
- Hypomagnesaemia
- GI complications – Dyspepsia, diarrhea, billiary tract disease
- Neurological complications – Tremor, peripheral neuropathy
- Hematological complications – Leucopenia, anemia, thrombocytopenia
- Osteoporosis

2. Rejection

- Acute cellular rejection
- Acute antibody mediated rejection
- Bronchiolitis obliterans
- Chronic lung allograft dysfunction other than BO

3. Infection

- Tuberculosis
- CMV
- Viral Hepatitis
- Pneumocystis pneumonia
- Aspergillus

4. Malignancy

- PTLD
- Skin cancer

Renal dysfunction and Electrolyte abnormalities

Nephrotoxicity is a well-recognized side effect of chronic calcineurin inhibitor exposure[1, 2]. A significant proportion of transplant recipients will experience acute kidney injury which results from the decreased blood flow as a consequence of afferent and efferent renal arteriole vasoconstriction. Due to adverse effects on the renal tubules and chronically decreased renal blood the incidence of chronic kidney disease and end stage renal disease are high following transplantation[3, 4]. Electrolyte abnormalities including hyperkalemia and hypomagnesaemia due to CNI therapy are frequently encountered following transplant. Regular monitoring and management can prevent serious consequences including mortality following major electrolyte derangements.

Metabolic complications

Chronic steroid and calcineurin inhibitor administration impairs glucose metabolism, causes hypertension and hyperlipidemia. Diabetes mellitus is present in 33.5% of the recipients at 5 years after transplantation[5, 6]. Weight gain and obesity are highly prevalent complications following transplantation. Identification and proper management of these complications can prevent cardiovascular morbidity and mortality. Osteopenia and osteoporosis are frequently encountered in transplant recipients due to accelerated bone demineralization. Interventions to improve bone density can prevent osteoporotic fracture and its associated morbidity[7, 8].

Bacterial infection

Bacterial infection is the most common infectious complication following lung transplant[9, 10]. A majority of them happen in the first 3 months after transplantation[11]. Pneumonia is the most frequent, followed by surgical site infection, empyema, sternal osteomyelitis, line sepsis, urinary tract infection and Clostridium difficile infection[12]. Reactivation or primary infection from tuberculosis is common in the endemic region and carries a high risk of mortality if not detected at an early stage. The risk for hospital acquired drug resistant bacterial infections predominate in the immediate post-operative period and the late infections are usually due to community acquired organisms.

Cytomegalovirus disease

Historically, CMV was associated with significant mortality and morbidity post lung transplant[13]. However with the current prophylactic strategy there has been a decline in the mortality. But the disease still contributes to significant morbidity and also increases the risk of chronic rejection of the lungs. It can present with a wide range of clinical manifestations including nonspecific constitutional symptoms, pneumonitis, esophagitis, hepatitis, colitis and bone marrow suppression. Either a universal prophylactic strategy or a preemptive strategy is used in the prevention of the disease. Most centers do universal prophylaxis for a pre specified time following transplant rather than monitoring the CMV viral load and administering therapy only if there is viral replication[14, 15]. After discontinuation of prophylaxis, monitor CMV PCR once monthly for three months followed by once in 6 months.

Aspergillus infection

Pulmonary aspergillosis is a serious complication following lung transplant[16]. Various factors unique to lung transplant make the recipients highly susceptible to aspergillosis[17]. The risk is even higher following large dose steroid induction and T-Cell depletion therapy. Aspergillus tracheobronchitis results in a tissue invasive disease of the airway and is associated with dehiscence, bronchial stenosis or bronchopleural fistula. The second and the more serious variant of aspergillosis in transplant recipients is Invasive pulmonary aspergillosis[18]. It causes radiographic opacity, dyspnea and respiratory failure and associated with a high rate of mortality in extensive disease. Surveillance bronchoscopy and identification of Aspergillus colonization can predict the subsequent risk for invasive disease.

Acute rejection

Acute rejection contributes to significant morbidity in the first post-transplant year. They also increase the risk for chronic rejection, which greatly affects the long term outcomes of lung transplant recipients. The acute rejection can be either acute cellular or antibody mediated rejection, each with distinct pathological pattern, cellular and molecular players[19]. The transbronchial lung biopsy can help in confirming the diagnosis and also grade the severity of rejection. Other modalities that can be used in the surveillance of rejection are peak flow monitoring, spirometry, chest x-ray and 6 minute walk test. The development of donor specific antibodies against HLA antigens can suggest the presence of antibody mediated rejection if there is concomitant lung function decline.

Hematological abnormalities

The combination of cell cycle inhibitor with calcineurin inhibitor can cause bone marrow suppression resulting in anemia, thrombocytopenia and neutropenia. This can result in serious complications if not identified in a timely manner. Valganciclovir and trimethoprim – sulfamethoxazole can have additive adverse effects on bone

marrow function. In addition to the drugs, infections that are common in transplant recipients including CMV and parvovirus can precipitate blood cytopenia[20].

Post lung transplant monitoring protocol:

1. *Daily monitoring of Weight, blood pressure, heart rate, oxygen saturation, temperature and peak flow at home.*It helps to confirm cardio respiratory stability and to identify significant impairment of graft function that may warrant further evaluation.
2. *Fasting capillary blood glucose* – Once weekly unless indicated otherwise.
3. *Clinic visit*

   Once weekly for the first month

   Biweekly for the 2nd month

   Monthly until 6 months

   Once in three months until 1 year

   Subsequently the follow up can be half-yearly.

The assessment will be focused on symptom evaluation to check for tolerance of post transplant drugs, nutrition and progression of physical fitness. The importance of protective measures to prevent infections can be addressed along with the review of the screening blood works and imaging studies.

4. *Laboratory testing for CBC with differential, sodium, potassium, magnesium, phosphorus, tacrolimus level, BUN and creatinine*

   Once weekly for the first month

   Biweekly for the 2nd month

   Monthly until 6 months

   Once in three months until 1 year

   Subsequently the follow up can be half-yearly

The goal is to identify and treat renal, metabolic and marrow toxicity of tacrolimus, mycophenolate, valganciclovir and septran at an early stage and prevent adverse outcomes.

5. *Chest X-Ray*

   Once monthly for 3 months

   Once every 3 months for next 9 months

   Followed by once in 6 months.

The recipient is at the highest risk for infection and rejection in the first 6 months following transplantation. A regular chest x-ray screening at this stage is a valuable tool in surveillance.

6. *Transbronchial biopsy and Broncheo-alveolar lavage with microbiology* – 1 month, 3 month, 6 month, 1 year.

After 1 year post transplant, the most common cause of mortality is chronic rejection. It is a progressive disease with very limited treatment options. There is some evidence showing that the identification and treatment of acute rejection may decrease or delay the development of chronic rejection. Surveillance biopsies to diagnose clinically imperceptible rejections may improve overall survival. In addition the bronchoscopic evaluation of the anastomosis and airway patency can be done to evaluate for aberrant healing of the graft airway. The broncheo-alveolar lavage can be used in conjunction with radiographic findings to identify colonization or infection of the graft.

7. *PFT and 6 minute walk test* – 1 month, 2 month, 3 month, 6 month and then every 6 months.

Functional assessments are used as tools for early identification of graft dysfunction that may warrant further studies.

8. *CMV PCR*- Once monthly for 3 months after discontinuation of the CMV prophylaxis. Then followed up half yearly.
9. *Donor specific antibodies* – Once in 3 months for the first year after transplantation.
10. *Liver function test, fasting lipid profile, urine analysis, HbA1C, fasting blood sugar*– Once every 6 months
11. *Annual surveillance* - CT Chest plain study, Tuberculin skin testing, HIV, HBsAg, Hep C, DEXA scan, mammogram, PSA, PAP smear and Ophthalmology visit.

TREATMENT OF REJECTION EPISODES IN LUNG TRANSPLANT

Definitive Therapy: Involves augmenting the immunosuppression

a) Hyper acute rejection
b) Acute Cell mediated Rejection
c) Acute Antibody mediated Rejection
d) Chronic rejection

Supportive Therapy: To ensure adequate oxygenation and haemodynamics – which can range from supplemental oxygen, mechanical ventilation to ECMO – depending on the graft function.

Definitive Therapy:

a) Cell mediated Rejection:
    a. Intravenous Pulse Methyl Prednisolone Therapy: 1 gram of Methyl Prednisolone given as an infusion over 1 hour for 3 consecutive days. *This high dose regimen is for average adults weighing 70 kgs. For patients weighing much less, eg. 35 kgs – half dose may be given.*
    b. After 3 days, the same dose of oral prednisolone to be recommenced as maintenance therapy
    c. To continue the usual maintenance doses of Tacrolimus and Mycophenolate
    d. For high grade rejection, severe graft dysfunction or recurrent rejection
        i. Alemtuzumab
        ii. Antithymocyte globulin(ATG)

b) Antibody Mediated Rejection(AMR): The following interventions are helpful depending on the severity of the graft dysfunction
    a. High dose steroids
    b. Plasmapheresis
    c. Intravenous IgG
    d. Rituximab
    e. Bortezomib

11. ROLE OF VADS:

Implantable left ventricular assist devices (LVADs) are presently accepted as a successful tool for bridging patients with end-stage heart failure to heart transplantation (BTT). As a result of an increasing shortage of suitable donor organs, waiting lists for heart transplantation (HTx) are growing in most countries as are support durations for VADs in BTT programmes or destination therapy.

The field of mechanical circulatory support (MSC) has made tremendous progress in the last two decades. Thousands of patients worldwide have undergone implantation of long-term MSC devices (MCSDs). Currently, management of patients with MCSDs has been guided by individual clinicians and center-specific protocols. There have been few randomized studies to guide patient selection and care of the MCS patient. Short-term success with MCS therapy largely depends on patient selection, surgical technique, and post-operative management. Long-term success depends on physician and patient engagement in excellent care of their device and personal health. The focus of these guidelines is long-term device therapy with the goal of patient discharge from the hospital. There is limited mention of short-term MCS support for acute shock patients. We acknowledge that most of the mentioned guidelines are either from European, Canadian and ISHLT (International society of heart and lung transplantation). We tried to make it simple to understand and practically can be implemented in this country. The purpose of these guidelines is to provide an impetus for organized dissemination of best practices from various centers with excellent outcomes in field of MCS.

Patients with either acute severe or chronic advanced HF with otherwise good life expectancy should be referred to a cardiac centre capable of providing MCS. Furthermore, patients awaiting heart transplantation who deteriorate or are otherwise not likely to survive until a donor organ is found should be referred for MCS.

Candidacy for MCS: Candidates are patients with advanced HF, including those, despite optimal treatment, continuing to exhibit NYHA IIIb or IV HF symptoms AND accompanied by MORE THAN ONE OF the following:

● LVEF □ 25% and, if measured, peak exercise oxygen consumption □14 mL/kg/min

● Evidence of progressive end organ dysfunction due to reduced perfusion not due to inadequate ventricular filling pressures

● Recurrent HF hospitalizations (> 3 in 1 year) not due to a clearly reversible cause

● Need to progressively reduce or eliminate evidence-based HF therapies such as ACE inhibitors or □-blockers, due to symptomatic hypotension or worsening renal function

● Requirement for inotropic support.

The gross management of heart failure patients should be done according to the INTERMACS profile at the time of presentation.

Table 1. INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) Scale for Classifying Patients with Advanced Heart Failure. [1]

Profiles	Definition	Description
INTERMACS 1	"Crash and burn"	Hemodynamic instability in spite of increasing doses of catecholamines and/or mechanical circulatory support with critical hypoperfusion of target organs (severe cardiogenic shock)
INTERMACS 2	"Sliding on inotropes"	Intravenous inotropic support with acceptable blood pressure but rapid deterioration of kidney function, nutritional state, or signs of congestion
INTERMACS 3	"Dependent stability"	Hemodynamic stability with low or intermediate, but necessary due to hypotension, doses of inotropes, worsening of symptoms, or progressive kidney failure
INTERMACS 4	"Frequent flyer"	Temporary cessation of inotropic treatment is possible, but the patient presents frequent symptom recurrences and typically with fluid overload
INTERMACS 5	"Housebound"	Complete cessation of physical activity, stable at rest, but frequently with moderate water retention and some level of kidney dysfunction
INTERMACS 6	"Walking wounded"	Minor limitation on physical activity and absence of congestion while at rest. Easily fatigued by light activity
INTERMACS 7	"Placeholder"	Patient in NYHA functional class II or III with no current or recent unstable water balance

NYHA-New York Heart Association.

If patient is in INTERMACS 1 or 2 they require extracorporeal short term device placement like intra aortic balloon pump, ECMO or CentriMag to stabilize.If patient is of profile 3 or 4 then either consider heart transplant if high chances of getting heart soon or long term ventricular assist device at the earliest after medical optimization. If patient is of profile 5 or 6 they can be on transplant list waiting for heart. If somehow don't qualify for transplant can be considered for LVAD in near future. INTERMACS 7 can be on drugs and will be kept on follow-up if condition deteriorates will be treated as above

Patient selection for permanent pump implantation.

1. All patients should have any reversible causes of heart failure addressed prior to consideration for MCS.

2. All patients referred for MCS should have their transplant candidacy assessed prior to implant.

Long-term MCS for patients who are in acute cardiogenic shock should be reserved for the following:

a) Patients whose ventricular function is deemed unrecoverable or unlikely to recover without long-term device support.

b) Patients who are deemed too ill to maintain normal haemodynamics and vital organ function with temporary MCS, or who cannot be weaned from temporary MCS or inotropic support.

c) Patients with the capacity for meaningful recovery of end-organ function and quality of life.

d) Patients without irreversible end-organ damage.

3. Patients who are inotrope-dependent should be considered for MCS because they represent a group with high mortality with ongoing medical management.

4. Heart failure patients who are at high-risk for 1-year mortality using prognostic models should be referred for advanced therapy including heart transplant, or MCS (bridge to transplantation [BTT] or destination therapy [DT]) as appropriate.

Risk management of co morbidities

-Recommendations for patients with coronary artery disease:

Patients being considered for MCS who have a history of coronary artery bypass grafting should have a chest computed tomography (CT) scan to provide the location and course of the bypass grafts to guide the surgical approach.

-Recommendations for patients with acute myocardial infarction:

If possible, permanent MCS should be delayed in the setting of an acute infarct involving the left ventricular (LV) apex.

-Recommendations for the evaluation of MCS candidates with congenital heart disease:

1. All patients with congenital heart disease should have recent imaging to fully document cardiac morphology, assess for the presence of shunts or collateral vessels, and the location and course of their great vessels.

2. Patients with complex congenital heart disease, atypical situs, or residual intraventricular shunts who are not candidates for LV support should be considered for a total artificial heart.

Recommendations for aortic valve disease:

1. Functioning bioprosthetic valves do not require removal or replacement at the time of implant.

2. Replacement of a pre-existing aortic mechanical valve with a bioprosthetic valve or oversewing the aortic valve at the time of implantation is recommended.

Recommendations for aortic regurgitation:

1. More than mild aortic insufficiency should prompt consideration for surgical intervention during device implantation.

Recommendations for aortic stenosis:

1. Patients with aortic stenosis of any degree that is accompanied by more than mild aortic insufficiency should prompt consideration for a bioprosthetic aortic valve replacement during MCS implant

2. Patients with severe aortic stenosis may be considered for aortic valve replacement, regardless of the degree of concomitant aortic insufficiency.

Recommendations for aortic root disease:

1. Patients with a history of vascular disease and/or coronary artery disease should have a pre-operative assessment of their ascending aorta for aneurysmal dilation and atherosclerotic burden with a CT scan prior to

implant.

-Recommendations for mitral valve:

1. Severe mitral insufficiency is not a contraindication to MCS and does not routinely require surgical repair or valve replacement, unless there is expectation of ventricular recovery.

2. Routine mitral valve repair or replacement for severe mitral regurgitation is not recommended.

-Recommendations for mitral valve stenosis:

Valve replacement with a tissue valve should be considered if there is moderate or worse mitral valve stenosis at the time of left ventricular assist device (LVAD) implantation.

-Recommendations for mechanical mitral valves:

1. Routine replacement of properly functioning mechanical mitral valve is not recommended.

-Recommendations for tricuspid valve regurgitation:

1. Moderate or greater tricuspid regurgitation should prompt consideration of surgical repair at the time of implant.

-Recommendations for infective endocarditis:

Device implantation in patients who have been bacteremic should have documented clearance of the bacteremia for at least 5 days on appropriate anti-microbial therapy. This anti-microbial therapy should include a total duration of at least 7 total days prior to MCSD implantation.

Absolute Contraindications:

Acute valvular infectious endocarditis with active bacteremia

Active infection of an implantable cardioverter defibrillator (ICD) or pacemaker with bacteremia

-Recommendations for intracardiac shunts:

1. Atrial septal defects, patent foramen ovale or VSD should be closed at the time of MCS implantation.

Recommendations for intracardiac thrombus:

1. Echocardiography or CT, with contrast when necessary, should be used pre-operatively to screen for intracardiac thrombus.

-Recommendations for atrial arrhythmias:

1. Atrial flutter or fibrillation is not a contraindication to MCS.

2. Patients with medically refractory atrial tachyarrhythmias may benefit from ablation of the arrhythmia or atrioventricular node (with subsequent ICD/pacemaker placement) prior to LVAD implantation.

-Recommendations for arrhythmia therapy:

Patients with treatment-refractory recurrent sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) in the presence of untreatable arrhythmogenic pathologic substrate (eg, giant cell myocarditis, scar, sarcoidosis), should not be considered for LV support alone, but rather biventricular support or a total artificial heart.

-Recommendations for peripheral vascular disease:

All patients with known atherosclerotic vascular disease or significant risk factors for its development should be screened for peripheral vascular disease (PVD) prior to MCS. Ankle –brachial index and peripheral Doppler are the tools used to screen PVD.

Peripheral vascular disease may be a relative contra- indication to MCS based on its extent and severity.

-Recommendations for life-limiting co morbidities and multiorgan failure:

Consideration of MCS in the setting of irreversible multiorgan failure is not recommended.

-Recommendations for pulmonary hypertension

All patients being considered for MCS should have an invasive hemodynamic assessment of pulmonary vascular resistance. Device can be considered for bridge to candidacy if PVR is high.

-Recommendations for neurologic function: [2]

1. A thorough neurologic examination should be performed on every patient being considered for MCS. Neurologic consultation should be obtained for patients with significant neurologic disease or dementia, or significant atherosclerotic vascular disease of their carotid or vertebral systems.

2. All patients being considered for MCS should have a carotid and vertebral Doppler examination as a screen for occult vascular disease.

3. CT scan or magnetic resonance imaging is warranted in patients with previous stroke to establish a pre-operative baseline study.

MCS is not recommended in patients with neuromuscular disease that severely compromises their ability to use and care for external system components or to ambulate and exercise.

-Recommendations for coagulation and hematologic disorders [(3)]:

1. All patients evaluated for MCS therapy should have a prothrombin time/international normalized ratio (INR), partial thromboplastin time, and platelet assessed pre- operatively.

2. Baseline abnormalities in coagulation parameters not due to pharmacologic therapy should prompt an evaluation to determine the etiology prior to implant.

3. Patients with a history of thrombophilia prior to MCS should have a hypercoagulable assessment before implant.

4. Patients with a clinical syndrome of heparin-induced thrombocytopenia should have confirmatory testing performed.

5. Thienopyridine anti-platelet agents should be stopped at least 5 days prior to surgery unless there is a compelling indication for continued use.

-Recommendations for malignancy:

1.Patients with a history of a treated cancer who are in long-term remission or who are considered free of disease may be candidates for MCS as BTT, with the involvement of an oncologist to determine risk of recurrence or progression.

2.Patients with a history of recently treated or active cancer who have a reasonable life-expectancy (42 years) may be candidates for DT if evaluated in conjunction with an oncologist to determine risk.

3.MCS as BTT or DT is not recommended for patients with an active malignancy and a life expectancy of 2 years.

-Recommendations for diabetes

1.Patients with poorly controlled diabetes should have a consultation with an endocrinologist prior to implantation.

2.MCS is relatively contraindicated in the setting of diabetes-related proliferative retinopathy, very poor glycemic control, or severe nephropathy, vasculopathy, or peripheral neuropathy.

-Recommendations for pregnancy:

1.Use of contraception in women of childbearing age after MCS is recommended.

2.MCS in the setting of active pregnancy is not recommended.

-Recommendations for age:

No Age limitation but Patients aged > 60 years should undergo thorough evaluation for the presence of other clinical risk factors that may decrease survival or quality of life after MCS.

-Recommendations for psychologic and psychiatric evaluation (4):

1. All patients should have a screen for psychosocial risk factors and cognitive dysfunction prior to MCS.

2. Family, social, and emotional support must be assessed prior to MCS.

3. Patients with a history of a significant psychiatric illness who are considered for MCS should undergo a thorough psychiatric and psychologic evaluation to identify potential risk factors.

4. MCS should not be performed in patients who are unable to physically operate their pump or respond to device alarms.

5. MCS is not recommended in patients with active psychiatric illness that requires long-term institutionalization or who have the inability to care for or maintain their device.
Recommendations for adherence to medical therapy and social network:

Assessment of medical compliance, social support, and coping skills should be performed in all candidates for MCS device implantation. Lack of sufficient social support and limited coping skills are relative contraindications to MCS in patients with a history of non-adherent behavior.

-Recommendations for caregiver burden:

1. Caregiver burden should be assessed prior to MCS implantation to assure that support will be available. Agreement on behalf of the patient is not sufficient.

2. Significant caregiver burden or lack of any caregiver is a relative contraindication to the patient's MCS implantation.

-Recommendations for antibiotic prophylaxis:

1. Patients should receive pre-operative antibiotics with broad-spectrum gram-positive and gram-negative coverage, as appropriate, prior to MCSD implantation.

2. Routine antibiotic prophylaxis should include at least 1 dose prior to surgery administered within 60 minutes of the first incision, remain in the therapeutic range throughout the duration of their use, and not extend beyond 24 to 48 hours.

-Recommendation for liver dysfunction

1. Patients with an elevated INR not due to warfarin therapy should be considered for treatment prior to MCSD implantation, and efforts should be made to optimize nutrition and right-sided intracardiac filling pressures. Short-term mechanical support, including extracorporeal membrane oxygenation, should be used in acutely decompensated patients who are failing maximal medical therapy.

-Recommendations for temporary MCS

The use of temporary mechanical support should be strongly considered in patients with multiorgan failure, sepsis, or on mechanical ventilation to allow successful optimization of clinical status and neurologic assessment prior to placement of a long-term MCSD.

-Recommendations for assessing RV function:

1. All patients should have an echocardiographic assessment of RV function prior to MCSD implantation. [L SEP]

2. All patients should have invasive assessment of intra- cardiac filling pressures prior to MCSD implantation, with a particular emphasis on RV haemodynamics. [L SEP]

3. Echocardiography assessment: includes Volume status Contractility,assess all valves/PFO,TAPSI, Apical to Annular distance,Ratio of RV to LV in short axis

-Recommendations for management of RV dysfunction:

1. Pre-operatively, patients with evidence of RV dysfunction should be admitted to the hospital for aggressive management, which may include diuresis, ultrafiltration, inotropes,

2. intra-aortic balloon pump, or other short-term mechanical support once optimized, RV function should be reassessed.

RV dysfunction post-MCS should be managed with diuresis, inotropes, and pulmonary vasodilators, including nitric oxide or inhaled prostacyclin. RV dysfunction refractory to medical management may require placement of a short-term or long-term mechanical RV support device. Phosphodiesterase 5 inhibitors may be considered for management of RV dysfunction in the setting of pulmonary hypertension after MCS.

-Recommendations for anti-coagulation and anti- platelet therapy post-MCS:

1. Anti-coagulation and anti-platelet therapy initiated post- operatively in the ICU setting should be continued with the aim of achieving device-specific recommended INR for warfarin and desired anti-platelet effects.

2. Bleeding in the early post-operative period during the index hospitalization should be urgently evaluated with lowering, discontinuation, and/or reversal of anti- coagulation and anti-platelet medications.

-Recommendations for infection prevention post- MCS therapy:

1. The driveline should be stabilized immediately after the device is placed and throughout the duration of support.

2. A dressing change protocol should be immediately initiated post-operatively.

-Recommendations for optimization of nutritional status:

1. Post-operatively for those unable to meet nutritional goals orally, feeding should be started early and preferably through an enteral feeding tube. Parenteral nutrition should only be started if enteral nutrition is not possible and under the guidance of nutritional consultation.

2. Pre-albumin and C-reactive protein levels can be monitored weekly to track the nutritional status of the post-operative patient. As nutrition improves, pre-albumin should rise and C-reactive protein should decrease.

-Recommendations for management of anti- coagulation and anti-platelet therapy for patients who present with gastrointestinal bleeding:

1. Anti-coagulation and anti-platelet therapy should be held in the setting of clinically significant bleeding.

2. Anti-coagulation should be reversed in the setting of an elevated INR and clinically significant bleeding.

3. Anti-coagulation and anti-platelet therapy should continue to be held until clinically significant bleeding resolves in the absence of evidence of pump dysfunction.

4. The patient, device parameters, and the pump housing (if applicable) should be carefully monitored while anti- coagulation and anti-platelet therapy is being withheld or the dose reduced.

-Recommendations for the evaluation and management of patients who present with a first episode of gastrointestinal bleeding: Class I:

1. Patients should be managed in consultation with gastroenterology.

2. Patients should at least have a colonoscopy and/or upper endoscopic evaluation.

3. If the result of the colonoscopy and/or upper endoscopic evaluation is negative, evaluation of the small bowel, particularly in those with continuous-flow devices, should be considered.

4. In the setting of persistent bleeding and a negative endoscopic evaluation, a tagged red blood scan or angiography should be considered.

5. Once the gastrointestinal bleeding has resolved, anti- coagulation and anti-platelet therapy can be reintroduced with careful monitoring.

Reducing the pump speed for continuous-flow pumps in the setting of recurrent gastrointestinal bleeding due to arteriovenous malformations may be considered.

Recommendations for the acute management of patients who present with a new neurologic deficit:

1. Assessment of current INR and review of recent INR is recommended.

2. Prompt consultation with neurology is recommended.

3. CT and angiography of the head and neck is recommended.

4. Review of pump parameters for signs of device thrombosis or malfunction is recommended.

5. Inspection of pump housing for clots in extracorporeal pumps is recommended.

6. Discontinuation or reversal of anti-coagulation in the setting of hemorrhagic stroke is recommended.

Assessing for the source of thrombus in the setting of an embolic stroke should be considered.

Selective use of an interventional radiologic approach to thrombotic strokes may be considered.

Selective use of thrombolytic agents in the setting of thrombotic stroke without CT scan evidence of hemorrhage may be considered.

-Recommendations for evaluation of MCS patients with a suspected infection:

1. In all patients, a complete blood count, chest radio- graphic imaging, and blood cultures is recommended.

2. At least 3 sets of blood cultures over 24 hours should be drawn, with at least 1 culture from any indwelling central venous catheters.

3. For those with a suspected cannula or driveline infection, obtaining a sample for Gram stain, KOH, and routine bacterial and fungal cultures is recommended.

4. When clinically indicated, aspirate from other potential sources, as dictated by presenting symptoms and examination, is recommended.

5. Directed radiographic studies based on presenting symptoms and examination are recommended.

Erythrocyte sedimentation rate or serial C-reactive protein should be considered.

-Recommendations for inpatient treatment of ventricular arrhythmias:

1. MCS patients with incessant ventricular arrhythmias require prompt admission for further management because hemodynamic compromise may occur.

2. Patients with ongoing VT refractory to medical therapy may require catheter ablation, which should be per- formed by an electrophysiologist with the requisite knowledge and expertise in treating patients with MCS.

-Recommendations for RV dysfunction after surgery:

Class I:

1. RV dysfunction after LVAD placement may occur as a late manifestation with symptoms and signs of right heart failure and changes in LVAD parameters, including a decrease in flows and pulsatility. Further evaluation should include an echocardiogram and right heart catheterization. Level of evidence: C.

2. When evidence of RV dysfunction exists, MCS patients may need to be admitted to the hospital for optimization, which may include initiation of inotropic support.

-Recommendations for device failure and malfunction [5]

1. Pump stoppage of a continuous-flow MCSD constitutes a medical emergency, and the patient should be rapidly transported back to the implanting center or another expert MCSD center for treatment.

2. Definitive therapy for pump stoppage is surgical pump exchange if the patient is stable enough to undergo reoperation.

3. Patients with a functioning pump, but with alarms or changes in parameters that cannot be resolved as an outpatient, may need to be admitted to the hospital for observation and close monitoring.

For patients who are unable to undergo surgery, the outflow cannula may be occluded percutaneously to halt the backflow of blood through the valve less outflow cannula as a stabilizing maneuver.

-Recommendations for management of the MCS patient during non-cardiac procedures:

1. The MCS team should be made aware when an MCS patient is undergoing a non-cardiac procedure so that collaboration between the MCS and surgical teams can take place.

2. For non-emergency procedures, warfarin and anti-platelet therapy may be continued if the risk of bleeding associated with the procedure is low. If therapy needs to be stopped, warfarin and anti-platelet therapy should be held for an appropriate period of time as determined by the type of procedure being undertaken and risk of bleeding. Bridging with heparin or a heparin alternative while a patient is off warfarin may be considered.

3. For emergency procedures, warfarin may need to be rapidly reversed with fresh frozen plasma or prothrombin protein concentrate. Vitamin K can be administered with caution, but has slower onset of action.

4. Post-procedure, warfarin and anti-platelet therapy may be resumed when risk of surgical bleeding is deemed acceptable. Patients may be bridged with heparin or a heparin alternative while waiting for the INR to reach the target range.

5. During minor procedures, blood pressure monitoring with Doppler is appropriate.

6. During procedures with risk of hemodynamic instability, an arterial catheter should be placed for blood pressure monitoring.

7. A central venous catheter may be placed for monitoring of central venous pressure and to administer drugs in the case of hemodynamic instability during surgical procedures of moderate or high risk.

8. During non-cardiac procedures, MCSD parameters should be continuously monitored by expert personnel such as MCS nurses or perfusionists.

9. A cardiovascular surgeon should be in the operating room or immediately available, especially in situations when the non-cardiac procedure is occurring close to the MCSD.

-Recommendations for evaluation of safety of the home environment:

1. An uninterrupted supply of electricity to continuously power the MCSD must be ensured. Outlets must be grounded, and the use of electrical extension cords or outlets with a switch should be avoided.

2. Patients should have a working telephone to allow outgoing calls in the event of an emergency and to allow the implanting center to contact the patient. The patient should familiarize himself or herself with paging the MCS team should an actual emergency arise.

Equipment at home should be placed in a configuration that minimizes the risk of falls, allows easy access to living and sleeping areas, and allows family members to hear alarms. Lighting should be adequate. The bathroom should be safe for showering with a shower chair, and have the appropriate toilet seat or any other necessary physical aids.

-Recommendations for the use of right heart catheterization:

1. Right heart catheterization is useful in the assessment of persistent or recurrent heart failure symptoms after MCSD placement and to evaluate for evidence of RV failure or device malfunction.

2. Right heart catheterization should be performed at regular intervals in patients being evaluated for or listed for heart transplant to document pulmonary artery pressures because irreversible pulmonary hypertension is associated with early allograft dysfunction/failure after heart transplantation.

Right heart catheterization should be performed to help corroborate evidence of myocardial recovery. The pulmonary artery catheter may be left in place with serial lowering of the pump speed to confirm acceptable haemodynamics with decreasing VAD support prior to pump explanation.

-Recommendations for management of atrial fibrillation and flutter:

Cardioversion of atrial fibrillation is recommended in patients with rapid ventricular rates that compromise device performance.

-Recommendations for management of ventricular arrhythmias:

1. Cardioversion is recommended for VT that results in poor device flows and/or hemodynamic compromise.

2. The occurrence of VT on MCS should prompt a search for reversible causes such as electrolyte abnormalities or drug toxicities.

Amiodarone is a reasonable chronic outpatient treatment to prevent recurrence of VT in patients with MCS. Therapy with b-blockade may be a useful in the setting of recurrent VT.

Recurrent VT in the setting of a continuous-flow pump should prompt consideration of a suction event. In patients with biventricular support with VF who are refractory to therapy, but have stable flows, the patient may be left in VF with the defibrillator function of the ICD turned off.

Emergency procedures for device malfunction or failure

Recommendations for emergency procedures with device malfunction or failures:

1. The patient and their caregivers should be trained to recognize MCSD alarms and troubleshoot emergencies prior to hospital discharge. This training should be delivered using both written materials and visual demonstrations, and emergency response skills should be tested before the patient and caregiver leave the hospital.

2. Ongoing refreshers should be provided to patients and caregivers at outpatient visits to ensure they remain competent in emergency procedures.

3. An emergency on-call algorithm should be established that patients and caregivers are familiar with so they may quickly contact the implanting center in the event of emergencies.

4. An emergency transport system should be established to expedite transfer to the implanting center in the case of emergency.

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