ST VINCENT'S HOSPITAL DARLINGHURST, SYDNEY
THE CURRAN FOUNDATION CARDIOTHORACIC ICU

Guidelines for Medical Staff 2021

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ROUTINE CARE OF THE POST-OP CABG AND VALVE SURGERY PATIENT

Initial assessment

The patients are transferred from the operating theatre by the anaesthetic staff with the help of a Scientific Officer. The staff should remain until the handover is complete and the patient is deemed to be stable. The following list gives the priorities post arrival:

1. Monitoring and haemodynamic Stability

The scientific officer and nursing staff transfer monitoring from the transport monitor to the ICU monitor. All parameters should be observed immediately to ensure the values are within acceptable limits. If the patient has an Intra-Aortic Balloon Pump, Extra Corporeal Membrane Oxygenation machine, Ventricular Assist Device or Total Artificial Heart in situ, this should be noted and details of the surgery and operative parameters should be recorded.

2. Handover

Anaesthetic: A detailed hand-over should include relevant past history and results of perioperative investigations (especially left and right ventricular function), grade of laryngoscopic view, the dose of sedatives, analgesics, muscle relaxants and other medications and the intraoperative course particularly the period coming off CPB (arrhythmias, pacing, defibrillation, inotropes, other support, bleeding). The current infusions should be identified and noted. Need for protamine and dose of protamine must be discussed with anaesthetist (to cover pump blood infusion).

3. Surgical

The surgeon or surgical registrar should hand-over the details of the surgery and any particular concerns. Instructions regarding anticoagulation post valve surgery should be given.

4. Examination

A detailed examination of the patient including airway, respiration, circulation, neurological systems etc should be performed. In addition, the urine output and amount of bleeding into chest drains noted.

5. ECG, CXR, ABG

The ECG should be performed off ventricular pacing if it is safe. It is most important to look for new changes consistent with ischaemia or infarct that may represent coronary graft occlusion. Significant changes must be brought to the attention of the CTICU consultant and surgical staff, as there may be an indication to re-explore the grafts or investigate by angiogram. This decision for invasive assessment will depend upon the nature, size and distribution of the ECG changes, the cardiovascular stability of the patient and perhaps the results of further investigation including echocardiography.
A supine CXR is performed as soon as practicable and is examined as soon as it is available. Note the position of the endotracheal tube and intravascular lines, the presence/ absence of a pneumothorax, extensive areas of atelectasis/ consolidation, pleural/

pericardial collections and/or pulmonary oedema. Specifically look for the 'deep sulcus' sign of a supine pneumothorax and if there is doubt regarding a pneumothorax then an erect CXR should be performed.

The initial ABG will help to determine the adequacy of ventilation, gas/blood flow matching and aid in the selection of FiO2. Also, note the potassium level and any acidosis (lactic or otherwise).

6. FBC, EUC, Mg, Ca Mg PO4, LFT, Coags

Usually performed soon after arrival once any blood or blood products have been given. A ROTEM may be performed if there is concern about bleeding. Mark bloods as urgent if patient is unstable.

7. Fluid Orders

Maintenance fluids consist of a 500ml bag of 5% Dextrose with 30mmol KCL and 20mmol MgSO4 at 20ml/ hr maybe prescribed. This is often avoided in patients with acute renal failure.

8. DVT Prophylaxis

Subcutaneous Heparin is administered if not bleeding, commencing next day

Routine postoperative medications

1. Antibiotics

Cephazolin 2g IV tds for total of 3 doses If allergic to penicillin or cephalosporins
Clindamycin 600mg tds for total of 3 doses
Teicoplanin 800 mg IV once for patients with MRSA colonisation or at risk and for patients with allergy to beta-lactams.

2. Analgesia

IV morphine infusion 30 mg in 30 ml normal saline or
IV fentanyl 300 mcg in 30 ml normal saline (particularly if AKI or obesity).
Paracetamol 1g q6hourly, initially IV then orally as soon as possible
/Panadeine Forte ii po qid depending on degree of pain/age/ Tapentadol IR 50 mg 6h prn etc. Ondansetron 4mg-8 mg slow IV q6h prn

3. Post-extubation:

Oxycodone 5-10 mg PRN q4h prn/Tapentadol IR 50 mg 6h prn +/- Morphine 5-10mg SC q4h prn Coloxyl with Senna ii po BD to prevent constipation.
Avoid usage of regular opioids unless history of chronic use (use prn only)

4. Stress Ulcer prophylaxis

PUD, HH, GOR or severely stressed patients need Pantoprazole 40mg IV daily 40mg po daily

5. BSL control

Insulin infusion initially, according to insulin infusion guidelines. In diabetics recommence usual medication at a reduced dose until eating well.

Anticoagulation

All post-op patients

- All patients require calf compressors to be applied. S/C heparin 5000 units bd or tds depending on weight, commencing D1 post op provided bleeding has stopped.

CABG patients

- Aspirin 150 mg stat on extubation, provided not bleeding, then 150 mg daily or 100mg EC daily if history of peptic ulcer disease, hiatus hernia or reflux.

Mechanical Valve Replacement patients

- Usually Warfarin Day 1 post op (day after surgery) provided bleeding controlled. Warfarin dose needs to be individualised and there is specific protocol for this. If patient was taking warfarin pre-op, start back on the old dosage.

Bioprosthetic Valve Replacement

- For aortic valves usually Aspirin on Day 1 postop.
- For all other valves (esp mitral valve) ask the C/T surgeon if warfarin is required.

Regular medications

- Pre-existing medications (e.g., for asthma, COPD, diabetes, hypertension, hyperthyroidism and so on) will be introduced as appropriate over the first few postoperative days.
- Beta-blockers maybe reintroduced on day 1 at half dose (pulse rate and BP permitting).
- ACE inhibitors are reintroduced as tolerated (monitoring BP and renal function).
- Lipid lowering drugs are recommenced. If not on any preoperatively, CABG patients should be started on Pravastatin 40mg nocte or Atorvastatin 20mg nocte.
- Nitrates are not reintroduced postop, as a general rule

Infusions on discharge

Infusions that are accepted on the ward are:

- Amiodarone
- Dobutamine up to 5mcg/kg/min

Ongoing Care and Common Postoperative Problems

1. Airway

ETT position is checked on CXR. The tip should be no further than half way down the aortic knuckle or projecting at the T3 level.

2. Ventilation

Many patients following elective heart surgery can be extubated in the first few hours after return from OT. The weaning process should begin when the patient is warm (>36.0C) & haemodynamically stable with bleeding controlled. The FiO2 should be reduced to a level that maintains a pSO2 of ~ 95-97%. The ventilator support is gradually reduced from an SIMV rate to the spontaneous mode of Pressure Support. The aim is to have acceptable respiratory parameters on PEEP 5cm H2O/Pressure Support 10cm H2O and FiO2 <0.4. Acceptable respiratory parameters for extubation are PaO2 > 80mmHg, PaCO2 < 45mmHg, TV > 7ml/kg, RR <24. If in any doubt, contact the CTICU Consultant. See also: CT ICU clinical practice guideline for Extubation.

V/Q inequality is the commonest cause of hypoxia and is due to intrapulmonary (or intra-cardiac) shunting. This hypoxia may be aggravated by a low cardiac output due to a decrease in the mixed venous PO2.

Causes include:

- Low lung volumes with airway closure and basal atelectasis.
- Intra-alveolar filling with fluid (Pulmonary oedema), WBC (pneumonia) or RBC (contusion)
- Small airway obstruction with bronchospasm
- Pneumothorax (especially tension) or haemothorax.
- Pulmonary embolism.

The approach to hypoxia or any respiratory emergency in the ventilated patient is to initiate the “Ventilator Emergency Drill” and find whether the problem is in the ventilator, the tube or the patient. Proceed as follows:

1. Disconnect the ventilator and manually ventilate the patient with a T-piece (“green bag”) at 15L O2 flow. If the patient improves the ventilator may be the problem.
2. Check the tube for obstruction by passing a suction catheter. There may be obstruction from secretions, kinking, biting, cuff herniation or impingement of the bevel. If suction and partial withdrawal do not relieve the obstruction, consider removal of ETT, bag-mask ventilation and re-insertion of ETT. Experienced airway operators should do this.

Also check for a cuff leak, which may be audible on bagging. This requires reinflation of the cuff or replacement of the tube if the cuff is ruptured. A short tube with the cuff between the cords is a common cause of cuff leak.

3. Check the patient for equal air entry. The causes of unilateral air entry are:
    - Tube down a bronchus usually the (R)
    - Pneumothorax/haemothorax
    - Massive collapse of lung.

Poor air entry both sides with watery or blood-stained secretions and high inspiratory pressures indicates pulmonary oedema.
Poor air entry with wheezing indicates lower airway obstruction due to asthma, CAL etc.

4. Urgent CXR and blood gas.

3. Circulation

Hypovolaemia

Hypovolaemia is common and often due to polyuria. It may be indicated by hypotension, cold peripheries, marked respiratory variation of the blood pressure with controlled positive pressure ventilation, low filling pressures (CVP < 6-8, PCWP<8- 10), low urine output (<0.5 ml/kg/h), tachycardia (>110/min), or CI <2.2. None of these is absolute and, probably, the most reliable method of assessing volume status is to check the response to a fluid challenge. If a 250- 500ml bolus of fluid improves the MAP with little change in filling pressures, then hypovolaemia is likely, and a further bolus may be appropriate. If the MAP does not rise at all and the filling pressures increase > 3mmHg, particularly if they are in the high normal range, then further boluses are unlikely to be helpful. Plasmalyte is the preferred choice of resuscitation fluid.

Bleeding can be “revealed” via the chest drains or “concealed” within the pericardial or pleural spaces. Excessive bleeding may have occurred in theatre. Many different guidelines have been proposed to address the issue of what is excessive bleeding. One that is easy to remember is the “4,3,2,1” guideline. Four hundred millilitres in the first hour, 300ml in the second, 200ml in the third and 100ml/h thereafter are the limits above which bleeding should give serious concern. This is only a guideline. Rate of blood loss should be taken into consideration. The Intensivist should always be alerted to any significant bleeding.

Similarly, transfusion of any blood products requires discussion with the Intensivist. The acceptable lower Hb limit depends on the general condition of the patient, rate and volume of chest drainage and haemodynamic stability and may range from 80 to 100 g/L. Other blood products are used depending on the perceived coagulation status and are ordered only in consultation with the ICU Consultant.

Management of bleeding may include, not necessarily in this order:

1. Informing the surgical team
2. Correction of hypocalcaemia
3. Reversal of Heparin with Protamine
   Protamine is given to cover the reinfusion of pump blood (100mg/bag of pump blood). Additional protamine may be required if the ACT is prolonged (eg. > 160 sec). However, excessive doses of protamine will prolong the ACT so it is important not to keep giving more protamine for a repeatedly elevated ACT.
4. Correction of coagulation factor levels with Fresh Frozen Plasma and Cryoprecipitate

5. Correction of thrombocytopenia and platelet dysfunction with platelets and DDAVP.
6. Antifibrinolytics – Tranexamic Acid
7. In severe situations activated factor VII
8. Beware of the sudden cessation of drainage that may be associated with cardiac tamponade.
9. ROTEM (thromboelastometry) & Multiplate (platelet function test) should be considered early for rational blood product use. The Intensivist in charge will need to be involved for these tests.

Vasodilation

Systemic vasodilatation is frequently seen in the early postoperative stage and can be due to:

- SIRS from the bypass is the commonest cause
- Rewarming
- Drugs - protamine, ACE inhibitors, SNP/GTN, paracetamol, sedatives Allergic reactions to blood products and plasma expanders.
- Sepsis
- Epidural anaesthesia

In general, vasodilatory shock is treated with addressing the cause, carefully titrated volume resuscitation initially and vasopressor drugs such as noradrenaline. In situations where the BP is refractory to noradrenaline, vasopressin should be considered.

Cardiogenic Shock

Cardiogenic shock post cardiac surgery requires consideration of peripheral perfusion, pulse rate, ECG, CXR and central venous pressure and often more invasive measures such as the Swan Ganz catheter or PICCO. The most critical investigation is urgent echocardiography, which allows visualisation of the pericardium, myocardium, and valves and may disclose luminal obstruction. Potential causes are:

a. Pericardial

Fluid (usually blood) accumulates around the heart and compresses the cardiac chambers. Clotted blood can selectively compress a single chamber of the heart. The typical picture is tachycardia with hypotension, poor perfusion and raised venous pressure. Oliguria is a key indicator of atrial compression. The CXR may show increasing size of cardiac silhouette but the critical investigation is urgent echocardiography. Be suspicious if inotropic support is relentlessly increasing in the early post-op period.

b. Myocardial

Many patients have pre-existing impaired ventricular function but acute deterioration can occur in the peri operative phase due to factors such as:

- Prolonged bypass time esp. if there is poor myocardial preservation
- Acute ischaemia
- Occlusion or kinking of grafts – usually detected on ECG changes

These patients often require myocardial support with:

1. Vasoconstrictor inotropes - adrenaline and noradrenaline
2. Vasodilator inotropes, - dobutamine, milrinone, levosimendan
3. IABP
4. ECMO support in some cases

c. Endocardial and Valvular

- Post infarct VSD
- Ventricular dilatation may cause increasing Mitral regurgitation.
- Artificial valves may leak or obstruct

d. Luminal Obstruction

- A “HOCM” type obstruction with systolic anterior motion of the mitral valve can occur in patients with LV hypertrophy on inotropes especially post AVR. Giving volume and weaning vasodilator inotropes rectifies this.
- Tension pneumothorax with obstruction to venous return.
- Acute pulmonary hypertension, which can threaten RV function, is treated with Nitric Oxide.
- Pulmonary embolism is rare in these patients.

e. Conduction tissue

- Bradycardia may require chronotropic drugs or pacing.
- Tachycardia may require antiarrhythmic drugs or defibrillation.

Atrial Fibrillation/Flutter

Atrial fibrillation/flutter is common post Cardiac Surgery (20-30%). The heart rate and degree of circulatory compromise needs to be assessed. Electrolyte and medical therapy is usually instituted first.

1. Potassium and magnesium supplements are given as indicated to put the levels into the high normal range.
2. Amiodarone is probably the most effective drug for reverting a patient to sinus rhythm and is thus favoured by most. It is given as an IV loading dose of 150 to 300mg over 30 min (if not previously on amiodarone), followed by an infusion of around 10mg/kg over 24h (commonly 900mg).
   Problems relate to its potential to produce severe bradycardia, heart block and QTc prolongation. Intravenous usage can lead to acute pneumonitis &/or acute liver dysfunction.
3. Digoxin can provide good rate control without being negatively inotropic but does not help revert patients to sinus rhythm.

If the circulation is severely compromised DC cardioversion is the quickest, most effective method of reverting a patient to sinus rhythm, but is not without risk

Ventricular Arrhythmias*

VT with a poor cardiac output is treated as a cardiac arrest with immediate DC shock (synchronised 200J) being the most important first response.

Non-sustained VT or VT with a good output may be treated first by ensuring airway, breathing and oxygenation is adequate, followed by checking appropriate electrolyte levels (principally K+ and Mg++). Drug therapy with Lignocaine, Amiodarone may be tried. It is important to question what may be causing or contributing to ventricular arrhythmias in a postsurgical patient. Arrhythmias may represent graft occlusion or tamponade. Pulmonary artery catheters and central lines may irritate the ventricle and cause arrhythmias.

Management of Cardiac arrest in these patients essentially follows the same principles as cardiac arrest in any patient, starting with the “ABC’s”. It may be most appropriate to give a DC shock to patients in VF or VT prior to commencing chest compressions in order to reduce potential damage to surgical repairs or grafts.
However, chest compressions should not be delayed if it is not possible to perform defibrillation within 30 seconds.

The standard protocol involves: three initial DC shocks – 200J, 200J, 360J; adrenaline 1mg every 3 min and Amiodarone as the first line antiarrhythmic drug at a dose of 5mg/kg (commonly 300mg) given over 3 min.

*** Remember, in the post-surgical patient, to notify the surgical team immediately of any patient with arrhythmias or haemodynamic instability, as the most appropriate management may be surgical, including re-opening/sternotomy in the ICU.**

***For bradycardia or cardiac standstill, if pacing wires are present, immediately connect them to the pacemaker and set pacing at rate of 80- 100/min.**

Hypertension

Sometimes it is necessary use antihypertensive medication in the early postoperative phase. GTN and Sodium nitroprusside are common infusions (intravenous hydralazine can be given as a bolus). Sedatives should not be misused for their blood pressure lowering properties if otherwise not indicated. Any intravenous therapy should be changed to enteral application as soon as appropriate. Pre-op nitrates and calcium antagonists prescribed for angina are not recommenced. Pre-op beta-blockers are recommenced as tolerated on Day 1 or Day 2, usually at half dose. Patients with recent myocardial infarction should be on a beta-blocker.

4. Neurology

Not all patients following cardiac surgery require infusion of sedatives. However, temporary sedation may be appropriate if patients are hypothermic (<36.0 C), paralysed or agitated. Propofol infusion allows for faster titration while midazolam infusion may be better tolerated in severely unstable patients.

Analgesia is of major importance for patients post thoracic surgery as pain can hinder adequate coughing, mobilisation and chest physiotherapy.

5. Chest drains

These are observed for blood loss and air leak. Blood drainage should show progressively smaller amounts with each hourly measurement. Drains are usually removed on Day 1, provided the drainage is <20mls/hour in the previous 24h and there is no air leak.

6. Renal/Electrolytes

Typically, there is a large diuresis in the early post-operative period that tails off to around 0.5ml/kg/h. Remember that diuretics are indicated for fluid overload and not for a low urine output per se. Potassium should be maintained in the upper reference range (4.5-5.0), however, care should be exercised with supplementation in those with renal impairment. Magnesium is also important and IV supplements of 10 - 20 mmols $MgSO_4$ infused over 1 2hours can be given for serum magnesium levels <1.0mmols/L).

7. GIT/Endocrine

Usually, patients commence a light diet on Day 1, post extubation. If intubation is prolonged, more than 2 days, NG feeding will be considered. Standard enteral feed is commenced at 30ml/h and, if the aspirate at 4 hours is less than 200ml, the rate is increased to 60ml/h and later adjusted according to the perceived needs as determined by the dietitian. Whilst the aspirates are less than 200ml/4h, the aspirate can be returned and the feeds continued. High BGLs are managed with an insulin infusion while in ICU according to the protocol. Diabetics should be placed back on their usual regime as soon as possible, perhaps with reduced doses for the first couple of days as most patients will have a reduced appetite. Otherwise, the total dose of actrapid used in the preceding 6 hours can be used to decide the dose of protaphane e.g., 2 units/h of Actrapid for 6 hours can be replaced by 12 units s/c BD of Protaphane. Metformin should not be reintroduced until good renal function is assured, as it is significantly renally excreted and can cause an intractable metabolic acidosis in the presence of renal failure.
The Endocrine Registrar should be consulted early for continuity of care on to the ward.

8. Hypothermia

Initial hypothermia is common. A Bair Hugger is used until the temperature is 36□C. Shivering increases myocardial oxygen demand and can be managed with additional sedation – Propofol/Narcotic. IV fluid warming therapy commenced in the operating room should continue in an unstable patient. Subsequent hyperthermia is common in the first 24-48 hours. Blood cultures should be taken if temperature >38.0□C.

9. Renal Dysfunction and Fluid Balance

It is firstly important to recognise the normal pattern of urine output post cardiopulmonary bypass (CPB). Frusemide and/or mannitol are part of the pump prime and patients commonly have excess water retention post-op resulting in an early diuresis. Cold diuresis can contribute. However, neuro-endocrine responses usually result in a low urine output after 12-24h (0.3-0.5 ml/kg/h) even in those with normal kidneys. In the early postoperative period, the intravascular space may be under filled despite total water excess. Commonly, on Day 1, the endeavour is to rid the patient’s body of excess water in the interstitial spaces but one must remember that diuretics can only directly extract fluid

from the intravascular space, and that the potential for rendering patients hypotensive or under perfused with over vigorous diuresis must be recognised.
Particularly in diabetics and those with some renal impairment it is not uncommon to have a transient rise in creatinine (few days) in patients who have undergone CPB. Contrast administered at recent cardiac catheterisation may contribute to the renal failure. There is no specific drug therapy for acute renal failure though diuretics can increase urine output. Frusemide does not decrease the duration of acute renal failure but may be useful in fluid management.

Renal replacement therapy (RRT) is generally instituted for the following indications:

- Fluid overload not responding to drug therapy
- Hyperkalaemia
- Uraemia (Urea > 30 mmol/l)
- Metabolic Acidosis

Please refer to ICU web under policies for full details of protocols for renal replacement therapy.

POSTOPERATIVE CARE OF PATIENTS UNDERGOING NON-TRANSPLANTATION THORACOTOMY

The majority of the admissions of patients undergoing non-transplantation thoracotomy (NTT) follow pneumonectomy, lobectomy, and drainage of an empyema or pleurodesis.

All NTT patients have compromised respiratory function, and may have cardiac disease.

Thoracotomy produces considerable pain that inhibits deep breathing. It discourages voluntary movement and may reduce the effectiveness of physiotherapy. Optimising pain relief, aids in the optimisation of respiratory function.

Initial Assessment

In most NTT patients, the endotracheal or endobronchial tube will be removed before admission to CT ICU.

1. Observation

All patients undergoing NTT receive supplemental O2 with the minimum therapy being 2l/min O2 via nasal prongs. The oxygen delivery should be checked immediately. Make a quick check of the airway, breathing and quality of circulation and assess the level of consciousness and discomfort, while the monitoring is being re-established.

2. Handover

2.1 From Anaesthetic Staff

A handover from the Anaesthetic staff is obtained regarding medical history and intraoperative management of the medical problems. The anaesthetic and surgical course during the operation is reviewed. The planned post-operative pain management is discussed.
An epidural catheter may have been placed and details regarding the site and placement, amount and type of local anaesthetic narcotic given, and suggestions regarding ongoing management should be obtained. If an epidural has not been placed, then PCA is the usual method of pain control. There will be some patients not suitable for either.

2.2 From Surgical Staff

A surgical handover is obtained, particularly regarding the exact procedure performed, any difficulties and the specific management of any drains e.g.

- low suction at –20cmH2O (never for pneumonectomy)
- no suction but vented
- clamped with intermittent opening (pneumonectomy)

3. Clinical Examination

A thorough examination of patient is performed including airway, respiration, circulation. If an epidural catheter has been inserted and a local anaesthetic agent has been administered, the extent of the block (as determined by loss of the cold sensation to ice on the chest and abdominal wall), and adequacy of pain relief is assessed. If necessary,

advice regarding management of the epidural should be sought from an Anaesthetic Registrar or Consultant.
The magnitude of air leaks and blood loss from chest drains is estimated. Unexpectedly large air leaks should prompt an immediate CXR and early notification of the surgical team.

4. Chest X ray

An upright CXR is performed as soon as practicable after arrival and examined as soon as it is available. Of particular interest in patients having had a procedure other than pneumonectomy is the degree of lung expansion particularly on the ipsilateral side and whether a pneumothorax is present. For pleurodesis to succeed, the lung must be fully expanded with no pneumothorax. For lobectomy and lung volume reduction surgery a satisfactory CXR should show fully expanded lungs with no pneumothorax. However, there may be some patients without enough residual lung to completely fill the intrathoracic space and some air space in the thorax is acceptable. The presence of a pneumothorax should prompt discussion with the surgical team as it may trigger further intervention or be treated conservatively depending on individual circumstances. In some cases, pulmonary atelectasis may prompt urgent physiotherapy or fibre optic bronchoscopy to clear airway obstruction by accumulated secretion. Occasionally this may occur in the non-operated lung that has been dependant during surgery.

The chest drain is kept clamped in patients who have had a pneumonectomy with periodic unclamping every hour for 1 minute.

In patients having had a pneumonectomy, the usual CXR will show the remaining lung fully expanded, the heart and mediastinal structures displaced slightly away from the remaining lung and an air/fluid level on the side of the pneumonectomy. Initially, the silhouette of the heart and diaphragm can be seen on the pneumonectomy side.
The fluid level rises to fill the pneumonectomised hemithorax over a period of about a week. If the level is higher than expected it may be due to blood loss.
A blown bronchial stump can cause a tension pneumothorax particularly in the ventilated patient. This will cause shift of the mediastinum away from the pneumonectomised hemithorax, which can lead to an abrupt decrease in venous return with hypotension, which should prompt immediate unclamping of the chest tube.

Conversely, if the chest tube is not clamped in a pneumonectomy patient the good lung and mediastinal tissues may herniate severely across to the operated side causing haemodynamic compromise – this is fixed by opening the chest tube to atmospheric pressure by removing the underwater seal. The Surgeon should be promptly notified if either of these circumstances occurs.

5. ABGs

ABGs need to be reviewed in the context of history and clinical assessment. Initial ABG should be compared if possible, with the preoperative values. It is important in some patients with chronic CO_2 retention not to elevate the PaO_2 beyond the preoperative level

as they may be dependent on a hypoxic drive for ventilation and an elevation of pO2 can lead to hypoventilation and hypercapnic narcosis. Some patients may have a chronically elevated pCO2 and this, coupled with postoperative analgesia may lead to an additional elevation of the PCO2. If this happens it should be discussed with the CT ICU Consultant .

6. Fluid Orders

As a general rule, IV fluids are restricted to a level that just maintains adequate cardiac output. Commonly, pneumonectomy patients are restricted to 1500ml/day. Excessive fluids may cause pulmonary oedema in the remaining lung.

Medications

1. Routine Regular

Antibiotics

Cephazolin 2g IV tds for total of 3 doses If allergic to penicillin or cephalosporins
Clindamycin 600mg tds for total of 3 doses
Teicoplanin 800 mg IV once for patients with MRSA colonisation or risk and for patients with allergy to beta-lactams.

Anticoagulant

S/C Heparin 5000 units bd or tds, depending on the weight commencing post insertion of epidural catheter and withheld 12-16h prior to removal of epidural catheter.

Analgesia

Epidural Ropivacaine 2mg/ml with Fentanyl 2mcg/ml at 4 -15 ml/h
or
PCA: Morphine 60mg in 60ml 0.9%Saline (NS) with PCA dose 1mg and 5 min lock out or
Fentanyl 1000 micrograms in 100 ml NS with PCA dose 20 micrograms + 5 min lock out
plus
Paracetamol 1 gm 6 hourly & Tapentadol IR 50 mg 8h prn.

2. Routine PRN

Anti-emetics

Ondansetron 4mg-8mg slow IV/IM q6h prn

3. Non-Routine

Analgesia

NSAID’s and Tramadol may be prescribed only in consultation with a consultant.
NSAIDS should be avoided with pleurodesis as they decrease the inflammatory response.

Ongoing Care

1. Pain Relief

Optimal management involves good pain relief with minimal or no sedation, hence epidurals are favoured. The risk of epidural abscess increases after 3 days and they are commonly removed after 3 days. If chest drains remain or if good pain relief is felt to be very important, an epidural may remain in situ for up to 5 days. Removal must be timed so that it occurs 12-16h-post s/c heparin. Adequate analgesia with regular Panadol or and prn oral oxycodone/IR Tapentadol and/or prn SC morphine should be charted. Again, NSAID and Tramadol may be prescribed at the discretion of the consultant.

If a PCA has been prescribed, this is usually continued until the chest drains are out and analgesic requirements have settled – usually 3 to 5 days. The appropriate protocols continue.

The Pain Team needs to be informed of all patients with PCA or epidurals in use prior to discharge.

2. Chest Drains

Lobectomy/Pleurodesis patients have their chest drains remain in situ on low suction, until there has been no air leak for 24h and the fluid drainage is less than 100ml/24h.

Chest drains in pneumonectomy patients are routinely left clamped, except for 1 minute each hour when they are unclamped during quiet breathing. They are generally removed the next day. An underwater seal drain must be connected at all times to the chest tube in case the clamp needs to be released urgently.

3. Respiratory Function

Chest physiotherapy is very important to help maintain good respiratory function. Expansion of the lung is checked with daily Xrays. Oxygen therapy is guided by the ABGs and SpO2 and desired targets chosen in the context of history and preoperative status as well as the current clinical status. Commonly SpO2 in the low 90’s is chosen as the target.

PERIOPERATIVE CARE OF THE LUNG TRANSPLANT PATIENT

Indications

1. Bilateral Sequential Lung Transplant

    - Cystic Fibrosis (CF) COAD
    - Bronchiectasis
    - Idiopathic Pulmonary Fibrosis Primary pulmonary hypertension

2. Single Lung Transplant

    - COPD
    - Idiopathic Pulmonary Fibrosis
    - α1 antitrypsin deficiency

3. Heart-Lung Transplant

    - Primary pulmonary hypertension
    - Eisenmenger's Syndrome/Congenital heart disease

Evaluation

The cardiopulmonary Transplant manual has the details of the work-up prior to transplant and include:

- Pulmonary function tests and ABG's
- Echocardiography and possibly coronary angiography
- HLA tissue typing, Autoantibodies and a cell panel
- Thoracoabdominal CT Scan

Matching

Matching is done according to ABO compatibility and size matching is principally based on the predicted total lung capacity. Cross match may not be available pre- transplant so should be checked ASAP to prevent risk of acute/hyperacute rejection which is antibody mediated. Be very aware of confidentiality issues and release no information regarding the identification of the donor.

Preoperatively

1. Clinical Assessment

Patients are assessed principally to determine any recent onset of problems that may increase the risk of transplantation or alter the management of the transplant. Of particular interest are current infections or deterioration in function. They also include

gastrointestinal problems, chest pain, neoplasia or renal impairment. The patient should be fasting!

2. Tests to be done

There are a number of “Transplant packs” on Xavier 10 containing tubes and forms for all the blood tests that need to be done. There are different packs according to what transplant is being performed and the age of the recipient. Essentially, the difference is that Heart or Heart-Lung transplant recipients under 55 can donate their heart valves.

- Pre-printed SydPath form no: 0072 – “Heart Lung Transplant pre- operative tests”.
- This includes FBC, Coags, EUC, LFT’s, BSL, CMP.
- X match 3 units packed cells.
- Swabs for MRSA, MSU if abnormal U/A, Sputum culture if productive cough present.
- CXR
- ECG – Not for Heart-Lung recipients.

3. Tests to be reviewed

- Recent culture results and antibiotic sensitivities
- Review CMV and EBV serological status

4. Medications

All immunosuppressive drugs are to be charted by the lung transplant team. Usually, the patient will need to be given a calcineurin inhibitor such as tacrolimus as well as mycophenolate. The exact drugs and doses should be discussed with the transplant team.

Medications:

a) In anaesthetic bay
   1. Methylprednisolone 500mg IV
   2. Antibiotics according to previous culture results
   3. If CMV mismatch (recipient –ve, donor +ve) give Ganciclovir 5mg/kg IV

b) Off CPB or reperfusion
   1. Methylprednisolone 500mg IV
   2. Antibiotic (second dose of beta-lactam)

Check Medchart under Protocol then Cardiovascular & Respiratory for latest updates.

Operation

The incision for a single lung transplant is the classic thoracotomy and for bilateral lung transplant is either the 'Clam-shell' or bilateral thoracotomies. Cardio-pulmonary bypass (CPB) may be used depending on severity of disease, clinical diagnosis and surgical preference. This is achieved by one-lung ventilation (OLV) via a double lumen endobronchial tube. Heparin 5000 units may be given to help prevent clot formation, and is usually reversed with Protamine.

Removal of the diseased lung is in the sequence: PA, PV's, Bronchus. Implantation of the donor lung is in the sequence: Bronchus, PV's, PA. There is a de-airing /flushing /reperfusion procedure, during which the potassium rich pneumoplegic washout may cause transient hyperkalaemia and associated arrhythmias

Problems that can arise during the operation include.

- Hypoxia and/or hypercarbia (often sputum plugging in CF patients)
- Pulmonary HT, RVF, systemic hypotension
- Dynamic hyperinflation of the native lung (single lung transplant recipients).
- Myocardial ischaemia, coronary artery air embolism, arrhythmias
- Reperfusion injury.

CPB may be planned from the outset in patients with primary pulmonary hypertension or when the surgery is expected to be very difficult, for example, due to adhesions. It may be instigated during the procedure due to some of the problems listed above. The relevance is that there may well be sequelae of CPB including a greater chance of bleeding and coagulopathy. There does not seem to be long term survival differences for recipients who received CPB compared to those that don't.

TOE may be done in the OR to rule out pulmonary vein anastomotic thrombosis.

N.G. tube should be placed in O.R. to avoid gastric dilatation and help manage gastroparesis, which is very common post op.

Initial Assessment in the CTICU

The initial assessment of patients post Lung Transplant is similar to that of other intubated and sedated patients arriving post-surgery as outlined in previous chapters.

1. Monitoring

Monitoring is transferred with the aid of the scientific officer and nursing staff. Parameters are observed.

2. Ventilation

Initial mode of ventilation is pressure control to limit the stress on airway anastomoses and other sources of air leak. A Fisher and Paykel humidified circuit is used.

Common initial settings are:
SIMV (PC) 10-20 cm H2O rate 10, PEEP 5cm H2O, Pressure support 10cm H2O. Nitric Oxide may be used at 10ppm. . The NO connector is placed on the exit side of the water bath.

3. Handover

A detailed handover should be obtained from the anaesthetic, surgical and transplant medical teams.
The aim is to find out the following:

1) The preoperative diagnoses, relevant past history, physical status, (e.g., Cystic Fibrosis patient, emaciated, on home O2 with multiresistant Pseudomonas).

2) The intraoperative course including difficulties with ventilation, whether performed on or off CPB and if off CPB whether heparin was given. Any current infusions should be noted, as should any particular concerns arising during surgery.

3) The general plan regarding sedation and pain management, ventilation strategy, drain suction, fluid and vasoactive drug management and medications to be given.

4) Whether a bronchoscopy was performed at the end of the operation. If not, it may be performed in ICU to check that blood or secretions are not occluding the large airways.

N.B. The organ donor's right to confidentiality must be respected when caring for solid organ transplant recipients. Identifiable details of the organ donor should not be recorded within the recipient's admission or other progress notes.

4. Examination

A full examination must be done soon after arrival and documented.

There are usually four chest drains placed after bilateral Lung Transplantation, two on each side. By convention, the drains inserted more Anteriorly are placed Apically and the drains inserted more towards the Back are placed Basally. These should be identified and checked for bleeding and bubbling.

5. ECG, CXR, ABG, FBC, Full Biochemistry, Coags

These are performed as soon as practicable after arrival.

The ECG is compared to preop ECG's. Significant changes must be brought to the attention of the CTICU consultant and surgical staff. Pericarditic changes are not uncommonly seen after BSLTx and are of doubtful significance but myocardial ischaemia of clinical significance may occur rarely. The CXR is examined particularly for pneumothorax and reperfusion injury, which is discussed later.

6. Fluid Orders

Maintenance fluid consists of a 500ml bag of 5% Dextrose at 20ml/h. If the patient has been on CPB, then 30mmol KCl and 20mmol $MgSO_4$ are added to the bag.
Boluses of plasmalyte are used to maintain intravascular volume but are usually restricted to the volume that just maintains adequate cardiac output. Commonly, the target CVP is <10 mmHg, taking into consideration the risk of reperfusion lung injury. Packed cells are not to be used unless discussed with the Intensivist. Be very sure to check CMV status, as CMV negative patients must receive CMV negative blood.

Medications

All medication prescribing is done in consultation with the Transplant Team. The latest update is found on MedChart in Protocols under Cardiovascular & Respiratory.

1. Immunosuppressive

a) Methylprednisolone 125mg q8h IV x 3 doses. Then change to prednisolone 1mg/kg/day in 2 divided doses, tapering according to transplant team instructions.
c) Tacrolimus depending on renal function over 24h as a continuous infusion.
d) Mycophenolate 1500 mg BD should be given as soon as able to take oral medications.
e) Basiliximab is given instead of tacrolimus in patients with renal failure.

2. Antibiotics

IV antibiotics, effective against known pathogens previously cultured from the recipient, are given according to Transplant Team instructions. Antibiotics are also often given as a result of swab or culture results from the donor. Other prophylaxis:

a) IV azithromycin 500 mg daily for 3 days then 250 mg PO daily
b) Bactrim DS once daily PO Mondays and Fridays – PCP prophylaxis.
c) Amphotericin (5mg/ml) 2ml Nebulised bd with Ventolin 2.5-5mg nebulised 30 min prior to amphotericin to reduce bronchospasm. (for aspergillus prophylaxis)
d) CMV prophylaxis for donor +ve/recipient –ve mismatch.
(i) Ganciclovir 5mg/kg IV Mon, Wed, Fri until changed to Valganciclovir orally.
(ii) CMV Hyper immunoglobulin on days 1, 2, 3, 7, 14, 21. Need approval from Red Cross Blood Bank.
e) EBV prophylaxis for donor +ve/recipient –ve mismatch. Valaciclovir 500mg po bd if not on Valganciclovir.

3. Others

a) Pantoprazole 40mg IV daily, changing to 20mg po bd when appropriate.
b) Insulin infusions are commenced when appropriate according to the standard protocol.

c) Pancreatic enzyme (e.g., Creon, Creon forte) as indicated for patients with Cystic Fibrosis. Pancreatic enzyme is given with tacrolimus to aid absorption in patients with CF
d) Coloxyl with senna ii nocte. Do not give lactulose or sorbitol, which generate gas in the bowel and aggravates colonic distention. Gastrografin 25-50 mls BD/TDS may be used in CF patients who have not opened bowels within 24- 48 hours of return to ICU.
e) Heparin 5000 u s/c tds (withhold prior to epidural insertion and removal)

Ongoing Care

Many of the aspects of the ongoing care of the Lung Transplant patients are similar to other cardiothoracic patients discussed in previous chapters.

1. Pain Management

Narcotic PCA (either morphine or fentanyl) is the preferred method. Supplementation with PO oxycodone is often useful. More complex pain management may require involvement of Acute Pain Team and include ketamine infusions, Tramadol etc.
Epidural analgesia may sometimes be considered. This is done by anaesthetists after coagulation has normalised. The usual solution used is Ropivacaine 2mg/ml with Fentanyl 2mcg/ml that comes in a 200ml bag. The infusion rate may vary between 4 and 14 ml/h. The degree of block can be assessed using ice with satisfactory analgesia generally corresponding to a block from T2 to T12.

2. Ventilation

Lung transplant patients are generally ventilated for at least four hours postoperatively where upon a decision is made, in consultation with the Intensivist, whether to proceed to extubation. This allows time for complications to be declared – principally reperfusion injury, bleeding or significant air leak.
A repeat CXR prior to extubation may be performed at 4 hours to check for evidence of re-perfusion injury.
Day 0-1 bronchoscopy is performed by the lung transplant team to look at the bronchial anastomoses and take specimens at the same time while doing a gentle bronchial toilet. Extubation may be planned in such a way as to accommodate this if possible. (Do not keep the patient intubated for a prolonged duration for the bronchoscopy, if in doubt discuss with the CTICU consultant and the lung transplant team).
The process of weaning ventilation is similar to other postop surgical patients with cessation of sedation and reduction of ventilatory support, with analgesia provided by epidural infusion or IV narcotics.
Nitric Oxide, if used, is weaned in a stepwise fashion before weaning of ventilation. Refer to Section V. Perioperative Care of the Heart Transplant patient.

3. Hypertension Control

There is an association between hypertension, calcineurin inhibitors and seizures – particularly in young women. Young patients on calcineurin inhibitors can have seizures if HT is not well controlled. Hypertension should be taken seriously in the post-transplant

patient. Pain control and ventilation should be assessed prior to starting antihypertensives.
Aim for the same blood pressure as preoperatively, usually systolic under 140 mmHg.

(i) GTN infusion in early postoperative period.
(ii) Hydralazine 5-10mg IV boluses may be appropriate for acute elevations later in the postop period (max 20mg/4h).
(iii) Diltiazem CD 180-240mg po daily is generally the first line oral agent.
N.B., diltiazem increases tacrolimus levels (see appendix)
(iv) Other antihypertensives as required.
(v) Hypomagnesaemia is a risk factor for hypertension related seizures in patients on CNIs.

4. Chest Drains

As mentioned previously, there are generally two drains placed in each hemithorax with the anteriorly inserted drains directed apically and the others basally. Drains are assessed daily by the transplant team and the surgeons make the decisions regarding drain removal. They are generally removed one at a time and the choice of drain to be removed first is based on which is the perceived greater problem – bubbling or fluid drainage. The remaining drain on each side can only be removed when there is no bubbling and the fluid drainage is less than 200ml/day.

Any sudden increases in bubbling or fluid drainage should be brought to the attention of the senior medical staff and prompt an urgent CXR.

5. Renal/Electrolytes and fluid balance

Renal impairment is relatively common in the transplant population and is usually multifactorial. There may be pre-existing renal impairment, drug insults (cyclosporin/Tacrolimus, aminoglycoside), sepsis or hypovolaemia as attempts are made to reduce lung water. In general, these patients are kept relatively “dry” with a low CVP.

6. GIT

Patients with Cystic Fibrosis usually require pancreatic enzyme with meals or N/G feeds and cyclosporin therapy but not with Tacrolimus. Cyclosporin is rarely used nowadays.

Pseudo-obstruction is common following lung transplantation due to vagal damage, aerophagia and opioid analgesia. It is aggravated by giving sorbitol or lactulose, which can undergo fermentation to produce more gas. Cystic fibrosis patients are prone to distal small bowel obstruction – “meconium ileus” type syndrome.

Gastrograffin (25-50ml BD – TDS) should be used if bowels are not open within 24 - 28 hours. Other alternatives include Glycoprep, Picoprep etc.

7. Endocrine

Diabetes is common among those with Cystic Fibrosis and is managed with an insulin infusion initially. Steroids contribute to the hyperglycaemia. Other regimes of subcutaneous insulin may be commenced when the patients are extubated and eating regularly, under the direction of the Endocrinologists.

Morbidity and Mortality following Lung Transplantation

Peri-Operative Morbidity

Complications are relatively common and include the following. Some of these will be discussed more extensively.

Early morbidity post lung transplant
Cerebrovascular ischaemia
CPB related cognitive dysfunction
Pulmonary vein thrombosis
Haemorrhage
Persistent air leak /surgical emphysema
Wound dehiscence
Anastomotic breakdown
Gastroparesis/ileus/pseudo – obstruction.
Phrenic nerve palsy
Reperfusion ischaemic injury
Infection
Renal dysfunction

Drug related complications are relatively frequent, the most important group being secondary to the immunosuppressives. The calcineurin inhibitors (cyclosporin and tacrolimus) commonly cause hypertension, renal dysfunction and hyperlipidaemia.

The adverse reactions of some other drugs have a predilection for transplant recipients including aminoglycoside toxicity and statin-related rhabdomyolysis. As the risk of renal impairment is so high in the transplant recipient, non-steroidal anti-inflammatory drugs are contraindicated.

Mortality Post Lung Transplantation

The cause of death after lung transplantation varies with the time post-transplant and it is therefore useful to group the mortality risk into operative, peri-operative (within 30 days), early

(within the first post-operative year), medium term (1-3 years) and late complications (beyond 3 years).

Cause of Death	Within 30 days	Within 1 year	Midterm 1 – 3 years	Late > 3 years
Non-Specific Graft Failure (NSGF)	38%	20%	18%	14%
Infection (non CMV)	35%	52%	30%	28%
Technical factors	12%	3%	1%	1%
Cardiac	11%	4%	4$	4%
Acute Rejection	2%	2%	3%	2%
Obliterative bronchiolitis (BOS)	1%	9%	35%	40%
Post-Transplant Lymphoproliferative disorder (PTLD)	-	4%	3%	2%
CMV	-	4%	2%	-
Malignancy	-	2%	4%	8%

Postoperative Problems of Particular Note

1. Reperfusion Injury

Reperfusion injury of variable severity is a cause of primary graft failure occurring in 10-20% of lung transplants. It usually presents within the first 24 hours and is characterised by poor gas exchange, decreased lung compliance and infiltrates on CXR that are generally perihilar but may be extensive. The differential diagnosis includes volume overload, rejection, pneumonia, pulmonary vein occlusion and aspiration. Management is centred on continuing ventilatory support and minimising central venous filling pressures. NO at 10ppm is a common adjunct as it improves oxygenation and reduces pulmonary artery pressures. In severe cases ECMO may be indicated.

2. Pulmonary Vein Thrombosis

Thrombus formation at the pulmonary venous anastomotic site after lung transplantation is rarely seen in this unit but may have catastrophic consequences, including graft failure and stroke. It is suspected if the recipient exhibits unilateral or bilateral lung infiltrates, haemodynamic instability or evidence of systemic embolisation. Transoesophageal echocardiography is the investigation of choice +/- CT with IV contrast.
Should the TOE display evidence of clot obstructing the pulmonary veins with demonstration of a high velocity jet, then the treatment options include anticoagulation and surgery. Given the

serious potential problems associated with the condition and treatment options, a multi-disciplinary discussion at the consultant level is warranted.

3. Post Transplant Infections

Early Infection

Bacterial pneumonia occurs most commonly and relates to immunosuppression, blunted cough reflex due to pain and lung denervation, poor lymphatic drainage, impaired mucociliary clearance due to diffuse ischaemic injury to the bronchial mucosa and perianastomotic stenosis. Bacteria that are particularly problematic in these patients include Pseudomonas aeruginosa, methicillin resistant Staphylococcus aureus, Burkholderia cepacia and Nocardia asteroides (rare).

The choice of prophylactic peri-operative antibiotics depends on pre-transplant sputum culture results in recipients and is further modified by donor bronchus swab cultures. Chlamydia pneumoniae PCR is isolated from bronchoalveolar lavage (BAL) fluid in 34% of patients within the first-year post-transplant. The isolation of Chlamydia within days post-lung transplantation supports the assumption that this organism may be donor acquired. Persistent infection appears deleterious to graft function and is associated with both rejection and obstructive bronchiolitis. This has led to the routine empiric administration of a macrolide antibiotic (Azithromycin) for prevention of Chlamydial infection.

Cytomegalovirus Infection

CMV seronegative transplant recipients are at the highest risk for developing severe infection with predominant lung and gastrointestinal manifestations. Lung transplant recipients who are CMV seronegative and who receive lungs from a seropositive donor are termed “CMV mismatched” patients. The prophylactic management strategy in these patients includes the transfusion of screened CMV negative blood products and the prophylactic administration of ganciclovir post-operatively. CMV hyper-immunoglobulin in the dose previously mentioned is now used routinely in this group. The current ganciclovir prophylaxis regimen for “CMV mismatched” patients is 5mgs/kg IVI daily Monday, Wednesday and Friday for 10 weeks or until Valganciclovir 450mg P.O. bd is commenced.

Aspergillus Infection

The ubiquitous Aspergillus frequently colonises diseased airways. In lung transplant recipients, there is however a substantial risk of invasive Aspergillus disease due to devitalised peri-anastomotic tissue and the presence of foreign suture material.

Prophylactic nebulised amphotericin is standard therapy in all patients. The isolation of Aspergillus from airway secretions mandates the prompt administration of oral itraconazole. However, failure to consistently clear the organism from airway significantly increases the risk of invasive disease and indicates the need to commence intravenous Amphotericin B or voriconazole. The dose for prophylactic amphotericin is 2mls (5mgs/ml) nebulised bd. Ventolin 2.5-5mgs is nebulised 1/2 hour prior to minimise risk of bronchospasm.

Other Infections

Cotrimoxazole is routinely administered prophylactically against Pneumocystis carinii. Other common opportunistic agents include Epstein-Barr virus (EBV), Varicella-Zoster, Human Herpes 8, typical and atypical mycobacteria.

Diagnostic Work up for Suspected Infection in Lung Transplant Recipients:

1. Blood cultures are routinely ordered if the patient is febrile. All intravenous lines are removed or changed, the tips of removed catheters are sent for culture.

2. Urine is sent for microscopy and culture and urinary catheters are removed or replaced as required.

3. If the patient has diarrhoea stool is sent off for MC & S, parasites and clostridium difficile toxin. Blood is sent off for CMV PCR-DNA.

4. Chest radiograph

5. Deteriorating lung function, suspect: -
   (a) Infection
   (b) Rejection

Infection may also be associated with increased sputum production, blood neutrophil leukocytosis, and radiological infiltrates.

Investigations include:

- Sputum for MC&S, TB, fungi and cytology
- Nasopharyngeal swabs for viral IFA if there are associated features suggestive of a viral respiratory tract infection. Viruses identifiable are:
- Influenza A/B, RSV, Para influenza 1,2,3 and Adenovirus.
- Bronchoscopy with bronchial washings +/- transbronchial lung biopsies depending on clinical indications. Bronchial washings are sent off for cytology, bacterial, mycobacterial, fungal and nocardia microscopy and culture and, when indicated, Respiratory virus IFA, Chlamydia PCR, and TB PCR can also be requested on the BAL specimen.
- CMV infection is associated with fever, deteriorating lung function, diarrhoea and other gastrointestinal symptoms, leukopenia and thrombocytopenia. Diagnosis is best made with blood CMV PCR. The diagnosis may also be confirmed from lung or gastric biopsy specimens.
- Atypical pneumonia serology – specify: Influenza A/B, Mycoplasma pneumoniae, Legionella, Chlamydia pneumoniae, Chlamydia psittaci.

4. Rejection

Acute Rejection

The greatest incidence of acute rejection occurs within the first 3 months after transplantation and all patients therefore undergo surveillance bronchoscopy and transbronchial lung biopsies in order to detect early, sub-clinical rejection at 3, 6 and 12 weeks post-operatively. Transbronchial lung biopsies may be undertaken when clinical deterioration including radiological infiltrates and/or a fall in spirometric values in excess of 10% occurs after considering the risk vs benefit. Early clues for rejection on the full blood count include eosinophilia and thrombocytosis. The Luminex test for antibody mediated rejection is also performed.

Treatment for Acute Pulmonary Rejection

Current histological classification of acute rejection is A0-4/B0-4 (A represents perivascular inflammatory cell infiltrate and B represents airway centred inflammation).

Grade of Rejection A0B0

No significant rejection

A1B0

No treatment unless clinically indicated.

A1B1

Oral steroid pulse of prednisone 1 mg/kg/day given and then taper.

A1B2, A2B1, A2B2

If first episode: -
Methylprednisolone IV 15mgs/kg/day (max dose of 1gm/day) x 3 days

If second or recurrent episode: -
Oral taper Prednisolone1mg/kg/day reducing by 5mg/d every 2nd day to 0.25mg/kg/day maintenance.

A3B0-4

Methylprednisolone IVI (as above) + oral Prednisolone taper.

Recurrent grade 3 consider mycophenolate, Tacrolimus (FK506), cytolytic therapy + plasmapheresis.

A4B0-4

IV Methylprednisolone (as above) +/- oral prednisolone taper +/- ATG, monoclonal Ab inhibitors, TLI, plasmapheresis.

With the more severe grades of rejection, the patient is usually readmitted to hospital. Close observation is important. Patient often requires transfer to CTICU. IV access must be obtained

and arterial blood gas measurements attended (off oxygen if possible). Recipients will require frequent measurement of SpO2 both on and off oxygen (if patient is unable to manage off oxygen, then omit the latter reading).

Humoral Rejection

Antibody mediated rejection may cause graft dysfunction in the absence of typical vascular rejection. This is generally diagnosed based on a “Luminex” test. Presence of C4d on biopsy samples is compatible with mild rejection, moderate if associated with tissue damage or severe if causing graft dysfunction. Treatment is with immunoglobulin IVIg, plasmapheresis and rituximab.

Chronic Rejection

Chronic rejection is manifest clinically by progressive airflow limitation and histologically as obliterative bronchiolitis (OB), a fibroproliferative process involving predominantly small airways.

OB is the major complication that compromises long-term quality of life and survival in patients after lung transplantation. It is associated with recurrent airway infection and accounts for 40% of all deaths in these patients after 3 years. The airflow obstruction is irreversible and early recognition is important in an attempt to implement management strategies that preserve lung function. Unfortunately, in contrast to acute rejection, histological confirmation by transbronchial lung biopsies has a reported sensitivity of only 17%. The diagnosis therefore depends upon demonstration of progressive airflow limitation and investigations to exclude other causes of airway disease, rather than histological confirmation of OB.

5. Malignancy

This is not a problem of early post transplantation.

PTLD (post-transplant lymphoproliferative disorders) is particularly common after lung transplantation and is a major risk in EBV naïve recipients. The prevalence of various types of malignancy post-transplantation is dependent on the post- transplantation period as follows:

	Within 1 year	At 5 years
PTLD	53%	17%
Cutaneous Malignancy	15%	56%

All EBV naïve patients are given valaciclovir or ganciclovir in view of supporting data which showed that this regimen reduced the risk of developing PTLD post-lung transplantation. The standard prophylactic dosage of valaciclovir is 500 mg bd

Valganciclovir is a suitable alternative, albeit more expensive.

PERIOPERATIVE CARE OF THE CARDIAC TRANSPLANT PATIENT

Background

Christian Barnard performed the first human heart transplant in 1967. In 1968, the first heart transplant in Australia was performed at St Vincent's Hospital, Sydney. Despite operative success, organ rejection prevented long-term survival. It was not until the early 1980's, following the discovery of cyclosporin that results dramatically improved. More than 80% of patients will survive 1 year, more than 75% will be alive at 5 years and about 60% of patients will be living at 10 years. The longest survival for an Australian heart transplant recipient is 30 years and going.

Indications

Cardiac transplantation is the treatment of choice for patients with advanced cardiac failure of any aetiology or severe angina with inoperable coronary artery disease. Specific indications include ischaemic heart disease, cardiomyopathy (mostly dilated) and congenital heart disease.

Inclusion criteria

- End stage symptoms (NYHA class III or IV)
- Symptoms despite beta-blocker therapy (or failed trial of beta blockers)
- No alternative therapy available.

Exclusion criteria

- Transpulmonary gradient (Mean PA-PCWP) >12 not reducible with vasodilators eg. GTN, SNP, PGI2 or inhaled nitric oxide. These patients may be suitable for heart-lung transplantation.
- Severe psychiatric disturbance, intellectual retardation or demonstrated non-compliance.
- Current alcohol or drug abuse
- Morbid obesity
- Malignancy
- Severe hepatic or renal dysfunction unrelated to cardiac disease, unless suited to combined organ transplant
- Immunodeficiency states e.g., HIV
- Active systemic infection
- Co-morbidity that prevents rehabilitation e.g., severe fixed CAL, disabling stroke.

Evaluation for heart transplantation

A full work up and evaluation is performed. This information is available on the ‘Heart Transplant Work-up Sheet’ in the front of the patients’ outpatient notes.

The management of the post-operative cardiac patient is in many ways similar to that of any other post cardiac surgical patient with a few noticeable differences which will be covered in this protocol.

The Transplant Procedure

Harvest of the heart is performed through a median sternotomy incision at which time the donor heart is inspected for coronary artery disease or congenital abnormality. After systemic anticoagulation with heparin, cardioplegia solution is administered into the coronary circulation and the donor heart is excised. The heart remains without oxygen until circulation to coronary arteries is restored after implantation of the organ in the recipient. Cardioplegic arrest, along with immersing the heart in cold preservation solution (e.g., Celsior) to provide topical hypothermia, provides adequate protection against ischaemic damage for 4 to 6 hours.

DCD heart transplants have been conducted at SVH since 2014. The ex vivo Organ Care System (Transmedics) involves the connection of the donor heart to a sterile circuit where it is kept beating and warm thereby limiting the detrimental effects of cold ischaemia that occurs with the standard organ preservation mode of immersing the heart in cold preservation solution. Once housed inside the portable device, the heart is reanimated, preserved and able to be functionally assessed until it is ready to be placed inside the recipient.

During orthotopic heart transplant the recipient’s heart is removed and the donor heart is inserted in its place in normal anatomical position. The native heart is excised by transecting the pulmonary artery, aorta and atria. Posterior and lateral walls of the atria and the atrial septum are left intact to serve as cuffs for the donor heart. The donor heart is implanted with atrial, aortic and pulmonary artery anastomoses.

Matching recipient and donor

Matching is done according to ABO compatibility (Rh factor not important). The donor must be of similar size and weight (preferably no more than 10kg heavier or lighter than the donor).

Recipient Perioperative Preparation

Patients are admitted through the Heart Lung Clinic during work hours (0800-1600) and through ED after hours. Depending on bed availability patients are then generally admitted to X10S or X10N. A CXR is performed in the A & E before transfer to the ward. There are a number of 'Transplant packs' on X10N and S. There are different packs according to the type of transplant being performed and the age of the recipient (these are all clearly marked).

Essentially, the difference is that Heart or Heart-Lung transplant recipients <55 years can donate their heart valves and therefore require the signing of a consent form and extra blood samples.

Test to be done:

- Pre-printed SydPath form no. 0072- 'Heart-Lung Transplant pre-operative tests'. This includes FBC, Coags, EUC, LFT's, BSL, CMP
- X match 3 units packed cells, FFP and platelets (4 to be in the hospital)
- MRSA swabs, MSU if abnormal U/A, sputum culture if productive
- Chest X-Ray
- ECG NOT required
- If patient < 55 years also use pre-printed SydPath form no 5600 and ensure consent form is signed.

Test to be reviewed:

- Recent culture results and sensitivities
- CMV and EBV serological status

Medications

Immunosuppression is complex and is only prescribed by the transplant team. In general, a combination of calcineurin inhibitor, mycophenolate and methylprednisolone is the triple immunosuppressive regimen used. As many heart recipients already have a degree of renal impairment pre transplant, cyclosporin/tacrolimus administration is titrated according to the patient creatinine (see appendix). Anti-thymocyte globulin or basiliximab may also be considered in patients where calcineurin inhibitors are undesirable.

Other considerations included CMV mismatch. This occurs when the donor is CMV+ and the recipient is CMV-. In such instances the recipient is administered prophylactic IV ganciclovir or oral valganciclovir (see appendix).

Physiology and Pharmacology of the Denervated Heart

At surgery, the sinoatrial (SA) node of the recipient is retained, but does not activate the transplanted heart across the suture line. The donor heart has its own SA node, which is not innervated. It is often possible to discern 2 P waves on the electrocardiogram. The donor SA node controls the graft rate. Hence, because of the absence of autonomic innervation, only drugs or manoeuvres that act directly on the heart will affect myocardial function e.g., valsalva manoeuvre or carotid sinus massage and atropine will not affect heart rate but drugs such as adrenaline, nor adrenaline and isoprenaline will exert a positive inotropic and chronotropic effect, beta adrenergic blockers will depress myocardial function. Digoxin will influence conductivity through its direct effect only. The denervated heart retains its intrinsic control mechanisms e.g., a normal Frank-Starling response to volume loading, normal conductivity and intact alpha and beta-adrenergic receptors.

The coronary arteries retain their vasodilator responsiveness to nitrates and metabolic demands. They can develop atherosclerosis but the patient may not experience angina with ischaemia or infarction because of the denervation
Denervation results most importantly in an atypical response to exercise, hypovolaemia and hypotension. Any increase in heart rate or contractility depends on an increasing venous return and circulating catecholamines and the response may be delayed. During exercise, muscle contraction increases venous return and the increased circulating catecholamines increase heart rate. This is a gradual response and as exercise ceases, the heart rate and cardiac output slowly fall as the catecholamine and the response levels decrease. In pathological states, the transplanted heart is especially dependent on adequate filling volumes, and attention to preload is a critical initial management step.
The denervated heart is also sensitive to extremes of heart rate: arrhythmia may cause serious haemodynamic problems. Atrial arrhythmias may be a sign of rejection. Amiodarone is usually safe and effective. Verapamil may precipitate profound hypotension and bradycardia because of the absence of the normal cardiac sympathetic–mediated response to vasodilatation. Adenosine used for SVT may induce asystole and profound hypotension in the transplanted heart and should therefore be avoided.
Despite this, a number of patients will develop reinnervation of their heart over a period of time.

Initial Assessment and Management

The patients are transferred from the OT accompanied by anaesthetist, scientific officer and surgeon who should remain there until the patient is transferred from the transport monitor to ICU monitor and the patient is deemed stable. The surgeon or surgical registrar should handover the details of the surgery and any particular concerns or management plans.

Initial management of the patient includes full examination of patient and taking note of the support patient is receiving, similar to all patients admitted to CTICU, who have undergone cardiopulmonary bypass.

1. Circulation

Particular note should be made of pulmonary hypertension and right heart function as this is a common problem due to the lack of pre-conditioning of the transplanted heart.
All hear transplant patients require AV sequential pacing and usually have extreme bradycardia or no underlying cardiac rhythm. Therefore, no attempt to perform ECG off pacing should be performed.

2. Renal

Patients are usually polyuric during the early postoperative period. However, transplant recipients often have a degree of pre-existing renal impairment due to chronic low cardiac output states, and may have received cyclosporin/tacrolimus preoperatively. These factors can lead to varying degrees of renal failure in the early postoperative period.
Aminoglycoside antibiotics should be avoided whenever possible. The dose of cyclosporine/tacrolimus may need to be adjusted or even ceased depending on renal function.

Ongoing management of the cardiac transplant patient

Ventilation and Nitric Oxide

Once the patient is normothermic, haemodynamically stable and bleeding minimally, ventilation should be weaned as per any cardiac surgical patient. Nitric oxide is frequently used in the post-operative management of cardiac transplant patients and is another consideration when considering extubation as the patient must be haemodynamically stable off nitric oxide prior to extubation.

Weaning of nitric oxide should be performed gradually in a stepwise fashion from 10 ppm to 5 ppm to 2.5 ppm and eventually off with careful observation of haemodynamic status. A fall in blood pressure, cardiac output, or a sudden rise in CVP, TPG, (mean PA- PCWP) can all indicate intolerance to weaning nitric oxide. Simply increasing the nitric oxide to its previous level will correct any haemodynamic changes.
Weaning from 10 ppm to 5 is usually well tolerated. As the nitric oxide delivery system is increasingly less accurate at low flows and the optimum dose is about somewhere between 2.5 to 5 ppm, small adjustments at these levels may produce haemodynamic instability. In the event of failure to wean nitric oxide other pulmonary vasodilators may be considered e.g., nebulised prostacycline or sildenafil.

Cardiovascular

1. Rhythm

Adequate heart rate (90) is managed by atrioventricular pacing. The donor heart will eventually develop a spontaneous rate of 70 -90 bpm. Occasionally a permanent pacemaker is required.

Underlying cardiac rhythm should be checked twice a day. This should be performed by slowly reducing the underlying pacing rate and observing the monitor. Rhythm strips and or a 12 lead ECG should be performed. Patients may be discharged to the ward whilst pacemaker dependent.

The pacing box is only turned off following discussion with a consultant. Always have the pacing box on a demand of at least 60bpm as a ‘back-up’. A-V pacing is preferred over atrial pacing due to high possibility of A-V conduction issues). Pacing wires are removed after the first cardiac biopsy (day 7) if no longer required.

2. Preload

An adequate preload is maintained by appropriate volume replacement based on LAP/PCWP and CVP measurements. Vasodilators (glyceryl trinitrate, SNP) help to control filling pressures in the first 2-3 days whilst myocardial compliance is still reduced. These are weaned slowly to avoid sudden atrial and ventricular distension. Higher filling pressures may be required initially because of post ischaemic reduction in ventricular compliance. Therefore, CVP should be maintained at 10 mmHg and LAP/ PCWP at 12 mmHg.

3. Cardiac Output

A cardiac index of >2.2 should be maintained with the use of inotropes such as adrenaline, dobutamine or milrinone. Large doses of adrenaline should if possible be avoided as this may lead to lactic acidosis and peripheral vasoconstriction. Milrinone (a phosphodiesterase inhibitor) has the advantage of being an inodilator but the dose has to be carefully titrated in renal impairment. Vasoconstrictors such as Noradrenaline may be required to treat the associated vasodilatation if hypotensive. Over a period of time these may be weaned. The exact process of weaning is usually decided in combination by the surgeon, transplant cardiologist and intensivist. Occasionally a 'post–pump' vasodilatory shock occurs and the treatment for this is the same as for a non-transplant patient with noradrenaline and/or vasopressin.

4. Hypertension

Hypertension can be a major problem in the postoperative patient. The aetiology is usually multifactorial, but one of the main causes is calcineurin inhibitors e.g., Tacrolimus leading to renal artery vasoconstriction. The newly transplanted heart is not trained and therefore untreated hypertension may lead to cardiac failure. In addition, patients are usually hypotensive pre transplant and abrupt rises in blood pressure to levels greater than 140mmHg systolic can cause hypertensive encephalopathy and seizures, especially in patients < 18 years of age.

Treatment is initially with vasodilators (SNP, hydralazine, ACE inhibitors). Calcium antagonists particularly diltiazem have a calcineurin inhibitor dose sparing effect.
They appear to be an ideal choice; however, it should not be initiated if there is a degree of AV block and only following discussion with the transplant cardiologist.

If haemodynamically stable, monitoring lines should be removed at the earliest opportunity, as the patients are prone to line infections due to immunosuppression in the early post-operative period.

Renal System

Renal failure is more common in the transplant recipient than in other cardiac surgical procedures. Pre-existing renal failure due to chronic low cardiac output states, long cardiopulmonary bypass times, and the use of calcineurin inhibitors are all contributing factors. Daily monitoring of urea and electrolytes is essential. Management is the same as for any other patient with renal failure with a few notable exceptions.

These include:

- Modification of the immunosuppressive regimen may be required to reduce the nephrotoxic effects of calcineurin inhibitors. Basiliximab is frequently used as initial immunosuppression to delay the use of calcineurin inhibitors (see appendix).

- Patients are frequently frusemide dependent preoperatively and large doses may be required in the postoperative period to maintain a diuresis. Occasionally ethacrynic acid is used as an additional diuretic.

Gastrointestinal

If prolonged intubation is anticipated a nasogastric tube should be inserted. This allows decompression and aspiration of stomach, delivery of medications and nutrition. Feeding should be as per standard ICU protocol.

Post-operative Bleeding

Bleeding can be a major problem is the immediate postoperative period. Previous sternotomy, long cardiopulmonary bypass times and preoperative patient use of aspirin and warfarin all contribute to the bleeding. Bleeding can occasionally be so difficult to control, that patients may return with a packed open chest. Management of bleeding includes:

1. Rewarming of patient and warming of blood products
2. Reversal of heparin with protamine.
3. Correction of coagulation disturbances with FFP + CRYOPPT.
4. Correction of thrombocytopenia and platelet dysfunction with platelets and DDAVP.
5. Antifibrinolytics – Tranexamic acid (or Aprotinin or Aminocaproic Acid- not commonly used).
6. In severe situations activated factor VII.

CAREFUL LIAISON WITH THE SURGEON IS NECESSARY AS PATIENTS FREQUENTLY REQUIRE RETURN TO THEATRE TO CONTROL BLEEDING.

REMOVAL OF CHEST DRAINS IS FOLLOWING DISCUSSION WITH THE SURGEONS. USUALLY AFTER THE PATIENT IS EXTUBATED.

Medications

All medication prescribing is done in consultation with the Transplant Team. The latest update of this is found in MedChart in Protocols under Cardiovascular & Respiratory.

Pre-transplant

- IV/PO Tacrolimus (omit if creatinine > 150)
- PO Mycophenolate mofetil 1.5 g
- IV Vitamin K 10mg if on Warfarin
- Tacrolimus is omitted if creatinine>150 and replaced with Basiliximab 20 mg stat in the anaesthetic bay

In Anaesthetic Bay

- If creatinine > 150 give Basiliximab (ATG 500mg over 4 Hours (refer to ATG protocol) is sometimes given as a renal-sparing agent-administer Phenergan (12.5-25mg) ½ prior to ATG)
- IV Methylprednisolone 500mg
- IV Ganciclovir 5mg/kg if CMV mismatch
- IV Cephazolin 1000mg

ICU

- 500mls 5% dextrose with 30mmols KCL and 20mmols MgSo4 at 20mls /hr- optional
- Inotropes as indicated
- 500mls 5% dextrose with 250 units Actrapid to maintain BSL 6 – 8 (see protocol)

Routine Medications

- If Cr < 140 Tacrolimus infusion 0.015 mg/kg/dose over 24 h or 1mg BD PO. If Cr > 150 Basiliximab 20 mg on D0 and D4
- PO/IV Mycophenolate Mofetil 1.5 g BD
- IV Methylprednisolone 125mg 8/24 x3 doses, then…

  PO Prednisolone 1mg/kg/day in 2 divided doses, tapering by 5mg every 2nd day to a single daily dose of 0.25mg/kg maintenance. If any doubts about gastric absorption,

replace with IV Methylprednisolone (dosing in a 1:1 ratio e.g., 40 mg PO Prednisolone=40mg IV Methylprednisolone succinate

- IV Cephazolin 1000 mg x 3 doses or according to cultures/donor swabs etc
- IV Pantoprazole 40 mg daily
- PO Bactrim DS, Monday and Friday
- PO Nystatin oral drops 1mL qid
- IV ganciclovir 5mg/kg Monday, Wednesday and Friday if CMV mismatch
- Heparin 5000 units SC BD or TDS commencing 8h post-op provided not bleeding.

PRN Medications

- Morphine 1 to 2.5mg IV prn
- Ondansetron 4mg IV q6h prn
- KCL 5mmols IV prn if K < 4mmol/L and 10mmols IV prn if K < 3.5mmol/L

Immunosuppression is complex & patients are frequently entered into trials, therefore immunosuppression is prescribed and managed by the transplant team. The current trend is to use ATG in preference over Basiliximab.

Daily Investigations

The following investigations should be performed whilst in the ICU:

- CXR, FBC, EUC, CMP, COAGS daily in intensive care
- Tacrolimus levels (trough) daily for the first week, if stabilised then routinely every Monday and Thursday and/or as indicated by transplant team
- ECG daily
- QID rhythm strips and PRN (i.e., if any rhythm disturbances)

Daily Routine

Please refer to the Cardiac Transplant Clinical Pathway for specific patient management from pre-operative to postoperative day 8. The general daily routine whilst in ICU consists of the following:

Day 0 - Day of surgery

- Atrio-Ventricular Sequential Pacing (AVSP) to maintain donor heart at 90-110bpm
- ECG
- Continual cardiac monitoring
- ½ hrly haemodynamic/neurological/ventilation observations for 6 hours, then hourly
- 1 hourly urine measurements
- ½ hourly ICC observations for 6 hours, then hourly
- IV analgesia, IV immunosuppression, IV antibiotic therapy
- Extubate as soon as appropriate

Day 1

- AVSP to maintain donor heart at 90-110bpm
- ECG
- Continual cardiac monitoring
- Remove drains as ordered by surgeons
- Clear fluids
- IV/IM PRN analgesia
- Sit out in chair Day 2
- Continual cardiac monitoring and QID rhythm strips (PRN as required)
- If in sinus rhythm for >24hrs decrease pacing demand rate to 60bpm, following consultation with the transplant team. DO NOT turn pacing box off completely
- 4 hourly haemodynamic observations
- Remove drains as ordered by surgeon

- Remove wound dressing and leave uncovered if dry
- Oral analgesia if appropriate
- Light diet, administer aperients
- Mobilise

Day 3

- Continual cardiac monitoring (telemetry if on ward) and QID rhythm strips (PRN as required)
- If SR, leave pacing box at a demand rate of 60bpm. DO NOT turn pacing box off completely
- 4 hourly haemodynamic observations
- Oral analgesia if appropriate
- Ward diet, administer aperients
- Mobilise

Please refer to the Cardiac Transplant clinical pathway for ongoing management.

Early Mortality in the Cardiac Transplant Recipient

Mortality in the early postoperative period is usually due to primary graft failure, rejection or infection.

1. PRIMARY GRAFT FAILURE

Primary graft failure is a condition where the donor heart fails to function and is related to a number of contributing factors. Ventricular dysfunction is often present as a result of the adverse effects of brain death on the donor heart and the global ischaemia that occurs during storage and transport. Such dysfunction may be manifest primarily by decreased compliance in addition to diminished contractile force. In particular, right ventricular failure may occur as the unprepared right ventricle of the donor heart has to perform work against the recipient pulmonary vascular resistance, which is generally elevated.

2. ACUTE CARDIAC REJECTION

Acute rejection occurs in the majority of cardiac transplant recipients within the first three months. The frequency of rejection episodes decreases considerably after this time to being negligible at 12 months.

Cardiac rejection episodes frequently involve minimal signs or symptoms. If suspected, they need to be reported promptly to the transplant team as cardiac transplant patients can deteriorate rapidly.
Signs and symptoms can include:

- hypotension
- exhaustion/ weakness (lassitude)
- low grade fever
- decreasing physical ability, shortness of breath
- nausea and/or vomiting
- loss of appetite
- tachycardia (particularly atrial arrhythmias), bradycardia
- fluid retention/rapid weight gain > 2kg in 24 hours
- abdominal discomfort or pain
- any other signs or symptoms of cardiac failure

MANAGEMENT OF REJECTION
Cardiac rejection is divided into four grades (International Society for Heart and Lung Transplantation, 1990). For more detailed explanation of the pathology associated with the different grades, see reference. Outlined below is the St Vincent's Transplant Unit's protocol for the treatment of acute cardiac rejection;

0 No Rejection

1 a & b Mild and Mild-Moderate Rejection

No treatment required.

2 No Grade 2

3 a Moderate Rejection

IV methylprednisolone (500mg - 1g) daily for 3 days if < 4 weeks post-transplant (or if haemodynamic compromise present).
If > 4 weeks post-transplant and no haemodynamic compromise present: Oral Prednisolone taper 1mg/kg/day in 2 divided doses tapering 5mg/day to maintenance dose.
Ongoing 3a rejection may require further treatment

Patient may or may not be readmitted. Decision is made on an individual basis.

3 b Moderate - Severe Rejection

IV methylprednisolone (500mg - 1g) daily for 3 days.

Ongoing 3b rejection may require treatment with alternative drugs/therapy. Patient is usually readmitted for treatment. Close observation is necessary.

4 Severe rejection or rejection with haemodynamic compromise

IV methylprednisolone (500mg - 1g) daily for 3 days.

Ongoing grade 4 rejection will require aggressive immunosuppressive therapy. The decision as to which regime to use is decided on an individual basis.
Patient is readmitted to hospital. Close observation is important. Patient often requires transfer to CTICU. Patient is to remain on bed rest initially, until otherwise ordered by transplant team. IV access must be obtained.
Patient will require cardiac monitoring. ECG is to be attended.

3. INFECTION

Infection is a major cause of mortality following cardiac transplantation. Infection is most likely to occur in the early post-operative period and after augmentation of immunosupression for rejection. In the first month after transplantation, infections are attributed to 1) continuation of presurgical infection, 2) transmission by the donor allograft, 3) the surgery itself and iatrogenic procedures, 4) early reactivation of viruses. Bacterial infection remains the most common cause of infection; however opportunistic organisms (viral, fungal, and protozoan) are also commonly encountered. The risk of infection within the intensive care can be reduced by strict adherence to infection control policies and guidelines and early removal of intravascular lines.

IMPORTANT INFECTIONS ARE BRIEFLY DISCUSSED BELOW

- BACTERIAL INFECTIONS

In general, bacterial infections in cardiac transplant recipients should be treated as they are in the non-transplant patients. The choice of antibiotic should be guided by positive microbiological cultures and following discussion with the microbiologists.

- VIRAL INFECTIONS

I. HERPES SIMPLEX

Herpes simplex (HSV) is the most common viral infection after transplant surgery. It frequently causes cold sores, oral ulcerations, genital ulcerations and rarely oesophageal and gastric ulceration that may lead to severe GI haemorrhage. A clinical diagnosis is enough to justify empiric treatment. Treatment is with oral or IV aciclovir.

II. CYTOMEGALOVIRUS

CMV is a member of the herpes group of DNA viruses. CMV infection may result from primary infection in a seronegative individual, reactivation in a previously infected individual or reinfection with a new strain. Primary infection occurs earlier in the post-transplant period and tends to be more severe than do cases of reactivation. Active CMV infection usually occurs around week 6 post-transplant and following episodes of rejection that require enhanced immunosuppression.

Organ involvement may include pneumonitis, gastritis, colitis, myocarditis, chorioretinitis, hepatitis, leukopaenia and anaemia (due to bone marrow suppression). Concomitant bacterial infection is common.

Diagnosis is made with viral DNA/ RNA assays or by identification of viral inclusion bodies on tissue biopsy. Treatment is with ganciclovir (see appendix). Prophylactic ganciclovir or valganciclovir is always given for CMV mismatch recipients.

- FUNGAL INFECTIONS

ASPERGILLUS

Infections with the aspergillus species most commonly involve the lung and often present as an asymptomatic nodule on the chest x-ray. Disseminated infection may involve the vertebral bodies, sinuses, pleura, brain and liver. Symptoms depend on the site of infection, but usually include fever and malaise. Disseminated infections are associated with very high mortality rates. The most common species to cause infection in immunocompromised patients is A. fumigatus.

Treatment is with amphotericin B or a triazole (eg. Itraconazole/voriconazole).

- PROTOZOAL INFECTIONS

I. PNEUMOCYSTIS

Of the protozoan infections Pneumocystis is the most common.

Pulmonary infection with Pneumocystis carinii is now uncommon since the introduction of prophylaxis with cotrimoxazole (Bactrim). The infection may occur any time from 6 weeks after transplantation.

Symptoms may vary from mild breathlessness with dry cough, fever and malaise to severe respiratory failure requiring ventilator support. Symptoms are classically more severe than suggested by the radiographic appearance. The radiographic appearance is typically of bilateral perihilar infiltrates.
Diagnosis is made following demonstration of the organism on bronchiolar lavage or induced sputum. Treatment is with Bactrim or pentamidine (if allergic to Bactrim). An intense inflammatory process accompanies the infection and steroids should be administered concomitantly.

II. TOXOPLASMOSIS

T. gondii infection can cause a severe, life-threatening disease with tissue invasion and dissemination in immunocompromised hosts. Donor transmission of primary T. gondii is a concern mainly for cardiac transplants because of the predilection of the organism for the myocardium. Treatment is with cotrimoxazole (Bactrim)

MEDICAL MANAGEMENT OF PATIENTS ON EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO), VENTRICULAR ASSIST DEVICES (VADs) AND TOTAL ARTIFICIAL HEARTS (TAHs)

The medical management of ECMO, VAD and TAH patients is complex and dynamic, involving specialties that include (but are not limited to) intensive care, cardiology, surgery, perfusion and respiratory medicine. In the interests of good patient care, it is therefore essential that the management of these cases is both collaborative and well- coordinated by senior medical staff. The first section of this chapter covers key aspects of the medical management of patients on ECMO support, while the second half addresses the management of VAD and TAH patients in the peri-operative, acute and then the ambulatory setting.

ECMO

Preparing for ECMO support

Prior to initiating either VA or VV ECMO, medical staff should be prepared to manage bleeding, hypotension and arrhythmias.
ECMO cannulation can cause significant bleeding, both due to local vascular damage and myocardial trauma. While right ventricular trauma with an ECMO introducer or cannula will likely be obvious at the time of cannulation, guide-wire perforation may present with delayed pericardial tamponade. Pericardial tamponade should be suspected if ECMO flow becomes unstable, despite normal or high central venous pressure.
While either echocardiography (either transthoracic or transoesophageal) or x-ray image intensification can be used to guide ECMO cannulation, echocardiography is also useful in the detection of complications (such as pericardial tamponade).

Initiating ECMO can cause significant hypotension due to acute haemodilution and vasodilation. Vasodilation occurs due to the release of cytokines that occurs due to contact activation of blood, producing a systemic inflammatory response syndrome.[1] Hence vasopressor agents should be immediately available, and their pre-emptive use should be considered in patients who are hypotensive before ECMO flow is commenced.
Initiating ECMO can also cause atrial and occasionally, ventricular arrhythmias. A defibrillator should therefore be immediately available.
Management of ECMO flow Access limitation
Access limitation causes falling or unstable ECMO flow (‘line shake’) due to excessive suction in the access line (typically below -50mmHg) and is a cause of haemolysis.
Access limitation can be treated by either reducing pump RPM and / or administering a bolus of intravenous fluid or vasopressors (to increase central venous volume).
However, repeated administration of fluid boluses can aggravate respiratory dysfunction. For patients with acute lung injury, the use of a restrictive fluid management strategy improves oxygenation and reduces the duration of ventilation and ICU stay [2]. Hence ECMO flow should be just sufficient to provide adequate respiratory or cardiac support. If high flows are required, an additional access line should be considered to capture flow from both vena cavae.
The management of decreasing ECMO flow depends on the underlying cause, which is summarised below:

VA ECMO flow management

The adequacy of VA ECMO flow is a clinical assessment of the level of native ejection, level of inotropic support, mean arterial pressure and evidence of adequacy of organ perfusion, including serial serum lactate measurements.
Near infrared spectroscopy (NIRS) is useful for cerebral monitoring during ECMO. In a study of 20 VA and VV cases, a reduction in NIRS of either 25% below baseline or < 40% could be improved by increasing mean arterial pressure, arterial oxygenation or ECMO flow in 16 patients (80%) [3].
In patients with minimal or no LV function, high VA ECMO flow rates are required to provide adequate global perfusion. However, because VA ECMO increases LV afterload, this can cause LV distension if there is any aortic valve incompetence. LV distension increases the risks of pulmonary oedema, pulmonary venous haemorrhage and delays myocardial recovery [4]. In these cases, inotropes should be administered to encourage LV ejection and in our experience, Levosimendan may be helpful. If this is ineffective, an atrial septostomy [5] or an LV vent (via an open, percutaneous [6] or minimal-access approach [7]) should be considered to decompress the LV. The use of an intra-aortic balloon pump (IABP) has been proposed to reduce LV afterload in this situation. However, this may only be effective in centrally cannulated patients. In peripheral VA ECMO, concurrent use of an IABP has been shown to decrease coronary blood flow and aortic root pressure [8].
These patients should also receive therapeutic levels of anticoagulants to prevent intracardiac thrombus formation, especially if there is minimal native LV function. Monitoring distal leg perfusion
Flow in the femoral back-flow cannula should be monitored with a flow probe (which is typically about 100-300ml/min). The use of NIRS sensors on the lower limb is also useful to monitor the adequacy of distal leg perfusion, and may facilitate the early identification of complications.[9]

VV ECMO flow management

Once ECMO has been established and the level of ventilatory support decreased, flows are then titrated to maintain gas exchange within a target range.
Respiratory management on VV ECMO

Once adequate ECMO flows have been successfully established, the level of ventilatory support can be markedly reduced.
For patients on VV ECMO, an ‘ultra-protective’ lung ventilation strategy is advocated to minimise ventilator-induced lung injury, though this is currently not supported by large scale studies. The goals of the strategy are to limit alveolar over-distension while minimising atelectasis, which can develop due to several factors (especially inadequate

PEEP and absorption of oxygen). Recommended ventilation setting is: FiO_2 < 0.6 (titrated to maintain an SaO_2 > 85%), tidal volume ≤ 4ml/kg (predicted body weight), plateau inspiratory pressure < 25cmH_2O, PEEP >10cmH_2O. The respiratory rate should
be titrated to maintain pH and arterial pCO_2 within normal limits. [10]

Interestingly, a recent retrospective study revealed an association between lower PEEP values (<12cmH2O) during the first three days of ECMO support and increased mortality.[11] However, further prospective trials are needed to assess the significance of this finding.

Maintaining adequate oxygenation on VV ECMO

The main determinant of systemic oxygenation in patients with severe ARDS is the ECMO flow relative to cardiac output. Adequate oxygenation can consistently be maintained if ECMO flow is more than 60% of cardiac output [12].

Patients with a high cardiac output may have refractory hypoxaemia despite high ECMO flow. The use of ß-blockers has been advocated to improve arterial oxygenation saturation in this situation (to increase the ratio of ECMO flow to cardiac output) [13]. However, the efficacy and safety of this approach has not been established. Although ß-blockers may improve oxygen saturation, they also decrease oxygen delivery (which is the product of cardiac output and oxygen saturation).

Blood transfusion (from a haemoglobin of 7.0 to 9.9g/L) improves systemic oxygenation in VV ECMO patients with a high cardiac output [14]. However, blood transfusion is also associated with an increased risk of several adverse outcomes in ARDS patients (including mortality [15]). Hence it has been recommended that the haematocrit during ECMO should be the same as for the general ICU population [16].

Mild therapeutic hypothermia (to 34C) improves oxygenation by decreasing tissue oxygen consumption, and has also been shown to decrease cardiac output and vasopressor requirements [14]. However, these potential benefits should be carefully weighed against an increased risk of sepsis [17].

Should hypoxaemia occur during VV ECMO, the following steps should be taken:

Ensure:

- pump flow is adequate (> 60% cardiac output)
- oxygenator is functioning correctly (outflow pO2 > 150mmHg)
- exclude recirculation between cannulae

Consider:

- increasing pump flow (insertion of second access cannula)
- increasing ventilation
- bronchoscopy
- drainage of pleural effusions
- cooling patient to 35ºC
- reducing cardiac output by sedation, beta blockade etc.

Management of hypercapnia on VV ECMO

In contrast to pO2, the main determinant of arterial pCO2 during VV ECMO is sweep gas flow. Decreased ECMO flow rate also influences pCO2, but only at flows < 2.5lpm in adults [12].

Hypercapnoea can be treated by:

- maintaining pump flow > 2.5 lpm
- providing high sweep gas flow (up to 10 lpm)
- increasing ventilation (consider bronchoscopy / drainage pleural effusions)

Although hypercapnoea can easily be corrected on VV ECMO support, rapid correction of hypercapnoea has been associated with an increased risk of intracranial bleeding. While of unproven benefit, it may be prudent to slowly increase gas sweep flow when commencing ECMO to minimise this risk [18].

Respiratory management: VA ECMO

For patients on VA ECMO who do not have ARDS, a protective lung ventilation strategy (high PEEP, low respiratory rate) has been advocated, but with higher tidal volumes (6- 8ml/kg) than VV ECMO [10].

Differential hypoxaemia

During femoral VA ECMO, retrograde ECMO blood flow meets anterograde native aortic blood flow. If the patient has severe respiratory dysfunction, the heart and brain may be perfused with deoxygenated blood from the native circulation, causing differential hypoxaemia between the upper and lower body.
Hence, the right arm is preferred for arterial blood gas analysis, and pulse oximeters should also be used on the right hand or forehead. Cerebral NIRS may also be useful in these patients.

To treat differential hypoxaemia, the following steps may be necessary:

- increase ECMO flow (consider insertion of a second access cannula)
- increase patient ventilation
- consider bronchoscopy / drainage of pleural effusions
- consider re-siting the return line from the femoral to the right subclavian artery
- consider converting to V-AV ECMO (e.g., return line flow to cannulae in femoral artery and superior vena cava)
- Consider central ECMO

Hypercapnoea on VA ECMO

The treatment of hypercapnoea is the same as for VV ECMO.

Anticoagulation:

Balancing the risks of bleeding and thrombosis

Contact of blood with ECMO circuitry promotes inflammation, activates platelets and coagulation.
While the use of “biocompatible” surface coatings (such as heparin, polymethoxyethyl acetate and phosphorylcholine [19]) ameliorates this inflammatory response, anticoagulants are routinely administered to reduce the risk of circuit thrombus formation.
Anticoagulation also reduces the risk of deep venous thrombosis, which ECMO patients are prone to because of prolonged immobilisation, large-bore venous cannulation and other patient-related factors [20]. Anticoagulation is especially important in patients on VA ECMO with minimal cardiac function to prevent intracardiac thrombus formation.
However, anticoagulation increases the risk of bleeding, which is a leading cause of morbidity and mortality in ECMO patients. While cannulation and surgical site bleeding has been independently associated with worse patient outcomes,[21] the most feared bleeding complication is intracerebral haemorrhage. From ELSO registry data on combined VA and VV cases, this occurred in 6.1% of paediatric and 4.0% of adult cases, of whom only 22% and 20% survived (respectively). The causes of bleeding on ECMO support are complex and multifactorial; including thrombocytopaenia, hyperfibrinolysis, disseminated intravascular coagulation and acquired von Willebrand Syndrome (AVWS)[22].

Heparin and alternative anticoagulants

Unfractionated heparin is the most widely used anticoagulant during ECMO. While heparin is cheap, easily titrated, monitored and reversed, it has several limitations. Heparin resistance can occur during ECMO due to decreased antithrombin III (ATIII) levels, which may not respond to ATIII supplementation [23]. Unlike direct thrombin inhibitors, heparin is ineffective at inhibiting clot-bound fibrin [24] and promotes both non-immune and immune- mediated (heparin-induced thrombocytopaenia- HIT) platelet activation and aggregation [25].
There are currently no evidence-based anticoagulation guidelines for ECMO support. Suggested heparinisation levels are to a target Activated Clotting Time (ACT) of 180-220 seconds or an Activated Partial Thromboplastin Time (APPT) of 1.5-2.5 times baseline. Anti-Factor Xa can also be used to monitor heparin, which (unlike APPT) provides a measure of heparin activity, rather than concentration [26]. Suggested Xa target range is 0.3-0.7 IU/ml [22].
The utility of point-of-care (POC) viscoelastic tests (using paired heparinised samples) to monitor heparin effect has been examined for both thromboelastography (TEG) [27]and thromboelastometry (ROTEM) [28]. For both devices, derived variables correlated poorly with ACT and APPT. However, they POC testing may be useful in the management of anticoagulation and coagulopathy during ECMO, especially following cardiac surgery. Because of the limitations of heparin, there is increasing interest in the use of alternative anticoagulants during ECMO, especially direct thrombin inhibitors (DTIs). DTIs may produce more stable and effective anticoagulation than heparin, because they are unaffected by fluctuating ATIII levels and because they inhibit both circulating and clot- bound thrombin. DTIs also do not cause HIT. DTIs used in ECMO include argatroban, lepirudin and bivalirudin, infused to a target APPT of 1.5-2.5 x baseline [29]. In a small retrospective study ECMO post cardiotomy, bivalirudin (0.03-0.05ug/kg/h) was a safe and effective alternative to heparin and was associated with decreased

bleeding [30]. However, DTIs are not reversible and are expensive, which currently limits their use in most centres to patients with HIT. More evidence is needed to support their routine use in ECMO. Finally, the requirement for continuous anticoagulation may be reduced or eliminated by advances in circuit coatings. For example, the heparin coating in current ECMO circuits leaches out within a few days. However, modified coatings that prevent this from occurring may eliminate the requirement for heparinisation.[31].

Drug therapy during ECMO support

The pharmacokinetics and pharmacodynamics of drugs given during ECMO may be affected by several mechanisms. These include haemodilution, decreased protein binding, circuit sequestration and altered hepatic and renal blood flow [32]. Lipophilic and highly protein bound drugs undergo significant sequestration in the circuit, whereas hydrophilic drugs are more affected by haemodilution and other pathophysiologic changes caused by ECMO [33].

Sedation

Deep sedation is usually required during ECMO support, especially if cough or excessive respiratory movement are causing access limitation. However, very high sedative doses may be required due to their altered pharmacokinetics.

The levels of highly lipid-soluble drugs such as propofol [34], midazolam, fentanyl [35] and dexmedetomidine [36] all fall rapidly after the initiation of ECMO due to circuit sequestration, which accounts for the increased doses of these agents. By contrast, morphine (which is hydrophilic) is not sequestered into the circuit and is a useful alternative to fentanyl if tachyphylaxis develops.

During weaning, the provision of adequate sedation while encouraging spontaneous ventilation can be challenging. This may be facilitated with the use of dexmedetomidine, which provides sedation without respiratory depression and allows the doses of other sedatives to be reduced [37].

Muscle relaxation

While a 48-hour course of muscle relaxants has been shown to improve survival from severe ARDS [38], prolonged use has been implicated as a potential risk factor for ICU - acquired weakness [38].

However, in practice it may be difficult to avoid prolonged use of muscle relaxants, especially in VV ECMO cases. Coughing during airway suctioning or patient repositioning can cause severe access limitation.

Infections and antibiotics

Severe infections occur commonly in ECMO patients (more than 15 per 1000 ECMO days) and increase the duration of ventilation post- ECMO and mortality. Their incidence increases with the duration of support [39], type of support (VA > VV, especially when instituted during CPR) and age. The commonest causative organisms are coagulase- negative staphylococci, Candida and Pseudomonas [40].

The diagnosis of infection may be delayed, because fever is attenuated by heat loss in the circuit and new onset sepsis can be mistaken for progression of underlying disease.

Nosocomial infection should be considered if any of fever, rising white cell count or increased vasopressor requirement occur, and appropriate cultures performed. While central lines can easily be replaced, ECMO cannulae should only be replaced if they are the obvious source of infection (and if this is feasible). Empirical broad- spectrum antibiotics (including antifungal agents) should be commenced before the results of microbiological cultures are obtained. While nosocomial infections should be aggressively sought and treated, routine administration of prophylactic antibiotics is not recommended (with the possible exception of patients with an open sternum).

There is limited data to guide antibiotic selection and dosing during ECMO. The volume of distribution (Vd) is increased for lipophilic agents such as voriconazole, ciprofloxacin and meropenem, hence higher doses may be required to provide therapeutic plasma levels [41]. However, antibiotics levels may be increased during ECMO due to decreased clearance, as has been demonstrated in patients with impaired renal function receiving meropenem [42]. To further complicate matters, highly protein- bound agents (such as ceftriaxone) have both reduced Vd and clearance on ECMO [43], while caspofungin,[44] vancomycin [45] and oseltamivir are relatively unaffected [46].
Taken together, these finding indicate that guidelines for antibiotic administration during ECMO should be developed based on population pharmacokinetics. When available, drug levels should also be monitored.
Investigations

Routine investigations for ECMO patients include chest X-Ray, full blood count, electrolytes, liver function test, fibrinogen and INR.
ACT or APTT are performed 6-8 hourly and plasma-free haemoglobin (PfHb) either routinely or on clinical grounds.
A recent study found that an acute increase in D-dimer levels (with falling platelet count and fibrinogen concentration) predicts oxygenator clot formation.[47]. These changes all reversed after the oxygenator was replaced. D-dimer levels should therefore regularly be monitored as part of the assessment of oxygenator performance.
Haemolysis: detection and management

ECMO can cause haemolysis due to increased blood shear stress. This may occur due to access limitation, which causes gaseous cavitation from high negative pressure excursions.

Haemolysis can also develop due to fibrin deposition in the centrifugal pump head, and due to deep venous thrombus formation within or around the access cannula.[48] Haemolysis increases plasma-free haemoglobin (PfHb), which is cytotoxic and implicated in acute kidney injury [49, 50]. PfHb scavenges nitric oxide, causing pathological vasoconstriction in regional circulations and impaired coagulation [51].
Haemolysis has been reported in 18% of ECMO cases, although severity was not reported [52]. Circuit changes due to haemolysis (defined as low- level if PfHb was 0.1- 0.5g/L and severe if > 0.5g/ L) are much more common in VV than VA ECMO cases (23% vs. 1% respectively, $p<0.001$) [53].
Clinical signs of haemolysis are red or dark brown urine, high potassium and acute renal failure.

If confirmed by PfHb measurement, the management of haemolysis includes:

- repeat PfHb measurement to exclude a spuriously elevated reading from inappropriate (i.e., rough) handling of the previous blood sample
- treat access insufficiency (increase fluid administration or decrease pump speed)
- ultrasound examination of access cannula to look for thrombus obstructing flow, If found, increase level of anticoagulation
- consider changing the circuit

Elevated lipids can cause spurious elevations of PFHb, hence hypertriglyceridaemia should be excluded in patients with unexplained haemolysis.[54].

Continuous renal replacement therapy

Continuous renal replacement therapy (CRRT) is commonly used during ECMO support, more often to treat fluid overload than acute kidney injury and electrolyte disturbances [55]. The combination of ECMO and CRRT is safe and effective, although it increases the risk of haemolysis. Separate vascular access is not required to provide CRRT, as the circuit can easily be plumbed into the ECMO circuit, either as a simple 'in-line' haemofilter in the return line or via a parallel CRRT circuit.
Although the inflow and outflow lines to a parallel CRRT circuit can be attached to Luer connectors in either the access or return lines of the ECMO circuit, attachment to the return line (i.e. distal to the pump) is recommended. This is to avoid the risk of accidental air entrainment into the negative- pressure access line when connecting the CRRT circuit, which will rapidly de-prime the ECMO pump.

Nutrition

Enteral nutrition is generally well tolerated in the majority of VV and VA ECMO cases. While feeding intolerance is more common within the first few days of support, this may be effectively managed with the use of prokinetic medications [56].
Weaning V-A ECMO:

For patients on VA ECMO, the decision to perform a weaning trial is based on a clinical assessment of arterial pulsatility, serial echocardiography, the level of inotropic support and end-organ function.
Weaning entails a clinical, haemodynamic and echocardiography assessment while ECMO flows are reduced to below 1.5lpm. Echocardiographic parameters that predict successful weaning from low ECMO flows are: LV ejection fraction > 20-25%, LVOT velocity –time integral > 10cm and mitral annular peak systolic velocity > 6cm/s [57].

Weaning VV ECMO

Unlike VA ECMO, weaning VV ECMO is straightforward. Once ventilation and oxygenation are acceptable at low inflating pressures and FiO2, the commonest weaning strategy is to progressively reduce, then cease oxygen flow to the oxygenator [58]. ECMO flow does not need to be decreased. Should the patient fail to be weanable due to tachypnoea, hypoxaemia or distress, oxygen flow can be re-established to the oxygenator.

Several weaning trials may be required in some patients, especially if they have been on prolonged support.
There is increasing interest in the use of ECMO in non-intubated patients, especially as a bridge to lung transplantation [59]. This avoids complications associated with prolonged ventilation and patients can even be mobilised with a double-lumen ECMO catheter in place [60].
Decannulation: VA and VV ECMO

Heparin does not need to be ceased prior to decannulation. Removal of arterial ECMO cannulae is performed surgically, for femoral arterial repair. Venous cannula can be removed at the patient's bedside, with a purse-string suture or local pressure alone.
When removing venous cannulae, it is important to ensure that the patient is positioned with the cannulation site dependent, to avoid the risk of air embolism.
Post-decannulation:

Deep venous thrombosis is common following ECMO (8.1/1000 cannula days [20]). Hence venous Doppler studies should be performed following decannulation.

Medical Management of patients with Ventricular Assist Devices and Total Artificial Hearts

In this section, we will discuss the medical management of patients with long-term ventricular assist devices (VADs) that are in current clinical use, which include second/third generation left ventricular assist devices (LVADs), biventricular assist devices (Bi-VADs) and the Total Artificial Heart (TAH). This has been divided into two sections: The peri- operative management, which will briefly include pre-operative and intra-operative considerations (excluding surgical technique) and focus on early post-operative care and the management of the ambulatory patient on mechanical circulatory support (MCS)
Pre-VAD assessment and optimisation

The key to obtaining the benefits of long term MCS and achieving good clinical outcomes includes careful patient selection with meticulous assessment and optimisation of organ function in the immediate pre-insertion phase.[61]

Assessment of right ventricular (RV) function

Adequate RV function following LVAD implantation is key to satisfactory device function, due to its dependence on the output from the RV to ensure appropriate filling. Several mechanisms contribute to make the RV particularly vulnerable to dysfunction in the post- implantation phase. The incidence of RV dysfunction following LVAD implantation has been reported to be up to 40%. [62] The factors implicated include a sudden increase in RV preload due to improved cardiac output from the LVAD, alteration in the RV geometry from septal shift to the left thereby lessening the contribution of the septum to RV contraction, pulmonary vasoconstriction from mediators following cardiopulmonary bypass as well as transfusion and potential for RV hypoperfusion during cardiopulmonary bypass.[63] In addition, there may be a degree of pre-existing fixed pulmonary hypertension from existing heart disease, which exposes the RV to an elevated afterload. Post-implantation RV failure can result in shock, arrhythmias, renal and hepatic congestion and dysfunction- all of which contribute to mortality and morbidity such as

longer hospital stay, increased rate of re- operation for bleeding, worse organ dysfunction and decreased likelihood for successful bridging to transplant.[64] The lack of availability of satisfactory short to medium term mechanical support devices to support the RV makes the situation more challenging. This makes the assessment following medical optimisation of RV function in the pre-operative phase an important part of the decision process around device selection (LVAD versus Bi-VAD/TAH) or temporary post-operative mechanical RV support. The assessment is a composite evaluation of various parameters as below-

Clinical

- Female gender
- Non-ischaemic aetiology
- Previous cardiac surgery

Laboratory

- Bilirubin>2mg/dL (34 µmol/L)
- Creatinine>1.9mg/dL (168 µmol/L)
- AST > 80U/L

Haemodynamic

- High central venous pressure (CVP)
- High transpulmonary gradient (TPG)
- High systemic vascular resistance (SVR)
- Systolic blood pressure (SBP) < 96mmHg,
- Right ventricular stroke work index (RVSWI) < 250,
- Cardiac Index (CI) < 2.2L/min/m2,
- Vasopressor requirement
-

Echocardiographic

- Severe tricuspid regurgitation (TR)
- RV short/long axis > 0.6
- Tricuspid annular place systolic excursion (TAPSE) < 7.5mm
- Severe RV dysfunction [64]

Fluid status and renal function

Renal function and trends should be monitored closely prior to MCS insertion. In case of renal dysfunction, an assessment needs to be made around whether this is a result of hypoperfusion due to the low cardiac output state alone and therefore reversible once the issue of perfusion is addressed. This may be assessed by renal ultrasound and vascular doppler and in some instances, histological information from a renal biopsy may be useful. Patients who are oliguric or fluid overloaded might benefit from an intense period of in- hospital optimisation with haemodynamic optimisation with inotropes, intra-aortic balloon pump and blood pressure management, aggressive diuresis and haemofiltration were indicated for fluid removal [65].

There are limited data available however on the role of specific medical therapies such as vasodilators and temporary mechanical support to optimise patients prior to LVAD surgery.

Hepatic function

Cirrhosis, portal hypertension and any clinical evidence of liver disease should be recognised as potentially increasing the risk of poor outcomes after LVAD insertion and therefore close evaluation, including a liver biopsy may be required. Hepatic dysfunction may also be related to RV dysfunction and the resulting congestion and therefore potentially signify a need for biventricular support.[66]

Management of bleeding risk

Efforts to minimise bleeding risk including reversal of anticoagulation and allowing washout of anti-platelet agents should be considered.[61] Assessment of gastrointestinal bleeding should be undertaken as this presents a significant risk in the post-implantation phase, particularly with rotary VADs.

Management of infection

Patients should be assiduously screened and treated for infection prior to VAD implantation, including a dental check. They should have all unnecessary lines and catheters removed prior to implantation. Optimisation of glycaemic control in diabetic patients in another important consideration.

Nutrition

Being a potentially modifiable risk factor, assessment of nutritional state including parameters like albumin and pre-albumin should be undertaken by the nutritional service and in cases of malnutrition, targeted nutritional optimisation, with an enteral feeding tube may be required.[65] In cases of severe malnutrition, surgery may need to be postponed to allow for nutritional optimization, although this may be challenging to achieve in the context of a low cardiac output state along with splanchnic venous congestion, which limits the ability to achieve progress in this area.

Anaesthetic considerations

Induction of anaesthesia

This period can be associated with risk of significant deterioration and drugs that are associated with minimal myocardial depression are desirable.
Monitoring

Arterial line, central line and pulmonary artery catheter (except in case of Bi-VAD or TAH) insertion are standard care for this procedure.

In addition, intra-operative transoesophageal echocardiography (TOE) is essential as it can identify the need for additional surgery such as closure of a patent foramen ovale (PFO), tricuspid valve repair, aortic valve repair or replacement, removal of intraventricular thrombi, as well as monitor the status of the right ventricle and enable titration of fluid and vasoactive drugs. Additionally, it assists with setting of pump speed for the LVAD while assessing the position of the interventricular septum (IVS) as well as orientation of the VAD within the left ventricle. It is also vital in the process of de-airing during weaning from cardiopulmonary bypass (CPB).
Use of vasoactive agents

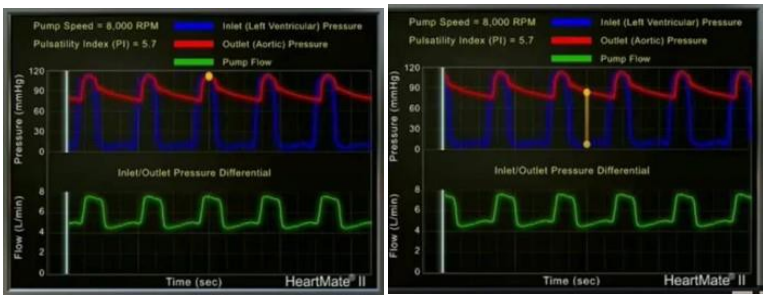
Separation from CPB can be a challenging time and generally requires inotropic support of the RV in case of LVAD implantation. Adrenaline and/or milrinone or dobutamine are used based on centre preference and experience. Adrenaline is generally recommended as a first line agent.[65] Although both dobutamine and milrinone are inodilators, milrinone is a phosphodiesterase inhibitor, which has reasonable pulmonary vasodilatory properties in addition to inotropy and may be less arrhythmogenic than dobutamine. However, its systemic vasodilatory properties limit the dose and generally require the use of a vasopressor concomitantly. Combining a phosphodiesterase agent with a beta-agonist provides better augmentation of RV stroke volume than either drug used alone, allowing lower doses to be used and thereby fewer side effects.[67] Levosimendan, a calcium channel sensitiser that acts independently of beta-receptors is used in some centres. It has a more sustained effect than milrinone and requires less adjunctive vasopressor support. However, due to its biotransformation to a potent, active metabolite which last up to a week, it is not infused for more than 24 hours and therefore there may be a benefit to an infusion 48 hours prior to surgery so that its effects are sustained through the early post-operative period. [68] Vasoconstrictors such as noradrenaline (predominantly a vasopressor with inotropic properties) or vasopressin (a pure vasopressor with less adverse effect on the pulmonary circulation) are frequently required in addition to maintain RV perfusion pressure as well as perfusion to other end organs.
Agents such as adrenaline and/or milrinone in addition to their use in RV support are used for their action on the LV to permit at least intermittent aortic valve opening. Again, expertise in TOE is invaluable during this phase.
Additionally, inhaled nitric oxide (iNO) or epoprostenol are generally used as selective pulmonary vasodilators to reduce RV afterload. If cardiac index is <2.0 liters/min/m2 and the CVP >20 mm Hg despite medical optimisation, a temporary RVAD should be considered before leaving the operating room. A CentriMag (Levitronix, Waltham, MA) or a paracorporeal Thoratec VAD (Thoratec Corp., Pleasanton, CA), are two of the most commonly used devices for temporary RV support.[65] In assessing the need of an RVAD, the proper function of the LVAD must be confirmed. Temporary ECMO support of the RV using a venous-pulmonary artery (V-PA) configuration is employed in our centre.

Early post-operative management

Pump settings

Typical pump speeds are 5000 to 6000 rpm for the HeartMate III, and 2400–3200 rpm for the Heart Ware HVAD. [61] When the speed is too low, there will be insufficient unloading of the LV. On the other hand, if the speed is too high, the LV decreases in size resulting in leftward septal shift and RV dysfunction, a suction event may result causing ventricular arrhythmias and finally

the decrease in LV pressure may completely prevent the aortic valve from opening. Details of titration of pump speed will be discussed in the next section.
The two key factors that affect flow across a cf-LVAD are (i) Pump speed and (ii) Pressure gradient across the pump [69]. Increasing the pump speed results in a higher flow, as more blood gets propelled through the device. The pressure gradient across the pump is the difference between outlet and inlet pressures i.e., that between the aortic root and the LV, with a large pressure difference resulting in decreased flow and vice versa.



During systole, denoted on the left sided panel with the yellow dot, the LV pressure rises and becomes identical to the aortic pressure. Because these two pressures are equal, there is no pressure gradient. As the pump inlet and outlet pressure becomes equalised it becomes easier for the pump to propel blood forward and therefore pump flow increases. This is shown by an increase in flow indicated by the green waveform. The reverse is true during diastole when the aortic and LV waveform separate as the pressure in the aorta becomes much higher than the pressure in the LV. This is shown in the right panel by the yellow line. Diastole is when the difference between the outlet aortic root and the inlet LV pressure is at its greatest. The pump must work against this increased pressure differential in order to propel blood forward and as a result, the flow decreases.

Lack of adequate preload with or without additional RV dysfunction or presence of tamponade can lead to the phenomenon of suck-down of the LV, which can lead to arrhythmias and further haemodynamic instability. Suck-down against the IVS may also occur if the LVAD inflow cannula is not appropriately aligned within the LV. Therefore, in the immediate post-operative period, speed is generally set to aim for relatively low pump flow (3.5-4.5 L/min in an average adult) to avoid the risk of suck-down.

Haemodynamic management

VADs are both preload dependent and afterload sensitive. It is therefore vital, particularly in this immediate post-operative period to ensure that the LVAD is provided with an adequate preload by optimising fluid status; ensuring adequate function of the RV with inotropy and considering the afterload sensitivity maintaining a systemic mean arterial pressure (MAP) no greater than 90 mm Hg.[65] In the case of the Heart Ware HVAD, an intrapericardial centrifugal pump, the recommended target for systemic blood pressure should not exceed 85 mm Hg.
The immediate post-operative period in the Intensive Care Unit (ICU) requires close attention due to rapid perturbations in haemodynamics that can occur. This may be due to bleeding, post cardiopulmonary bypass (CPB) diuresis and systemic inflammatory response, RV dysfunction, variations in pulmonary and systemic vascular tone and variable contribution of the LV to cardiac output. The cause of the instability, which may be due to a combination of factors is determined by a composite of clinical assessment, evaluation of parameters from monitoring

such as CVP, pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), cardiac index (CI) from pulmonary artery (PA) catheter, mixed venous oxygen saturation (SvO2) and pump flows and waveforms. Significant haemodynamic instability usually requires additional assessment with TOE to rule out surgical complications such as tamponade (see next chapter), but also assess for RV function, IVS position and the presence of suck down.
Additionally, the HeartMate devices provide a Pulsatility Index (PI) while the Heart Ware HVAD has a real time waveform display. The PI provides information of the contribution of native cardiac function to the overall output, with a low PI suggesting poor native LV function, excessive pump speed or hypovolaemia.[70]
These perturbations are generally less significant in patients with Bi -VADs or TAH although assessment and manipulation of the fluid status and of the systemic and pulmonary vascular resistance are still required and the risk of tamponade to the atria remains.
For the newer generation LVADs it is important to avoid high speeds, particularly in the early post-operative period as this results in excessive LV emptying. Second and third generation LVADs provide non-pulsatile flow and maintain a parallel circuit of flow out of the native aorta.[71]
Inhaled nitric oxide is generally maintained for at least 4-6 hours or longer if RV dysfunction is significant and then weaned gradually to permit liberation from mechanical ventilation although transition to inhaled iloprost and other pulmonary vasodilators may be required following extubation.
Inotropic support may be required to be continued into the post-operative period for up to two weeks as long as signs of RV dysfunction persist.

Mechanical Ventilation

Protective lung ventilation with a tidal volume of 6-8ml/kg ideal body weight with titration to maintain normoxia and normocarbia is recommended. The heart-lung interactions that occur during mechanical ventilation should be considered. Ventilating at functional residual capacity (FRC), avoiding hypoxia and acidosis will all minimise PVR and therefore RV afterload. Similarly, at the time of liberation from positive pressure ventilation the inevitable increase in preload to the RV and increase in afterload to the LV should be anticipated.
Transition to spontaneous breathing mode as soon as possible is favourable for haemodynamics and similarly minimising duration of sedation and mechanical ventilation to 4-6 hours post-operatively is ideal. This may however not be possible if significant instability or return to the operating room for complications is required.
Computer models of continuous-flow pumps have demonstrated a decrease in LV efficiency and an increase in RV efficiency with increasing positive intra-thoracic pressure. This offsets the increase in RV stroke work created by the continuous-flow pump. Therefore, patients may experience worsening of RV failure after extubation. The consequence of airway pressure and the interplay of ventilation and perfusion to RV performance should be considered when managing LVAD patients who develop respiratory failure.[72]

Fluid balance and renal management

Fluid management, particularly in the early post-operative phase is challenging as the balance between adequate preload to maintain VAD function and end organ perfusion must be balanced

by the fragile state of the right ventricle. Fluid boluses or blood products administered injudiciously, even in relatively small volumes, can result in a downward spiral of RV dysfunction from over distension and leftward shift of the interventricular septum. A rapid increase in CVP in response to a small aliquot of fluid may be used as a tool to guide administration suggesting limited RV compliance and potential over-distension.
Optimising the trans-nephric perfusion pressure with an adequate head of mean arterial pressure over potentially high existing venous pressure is another key consideration. Non-pulsatile circulation during CPB and haemoglobinuria from haemolysis related to prolonged CPB times can be additional insults to the kidney at this time. A urine output goal of at least 0.5ml/kg/hour is aimed for and preservation of renal function in the peri-operative period is an important determinant of good long-term outcome.
The standard indications of fluid overload, severe acidosis or uraemia and electrolyte abnormalities indicate the need for continuous renal replacement therapy, which equally may allow correction of over distension of the RV and limit high venous pressures thereby improving end-organ perfusion.

Nutrition

Early re-establishment of nutrition from the day after surgery is desirable. For patients unable to meet nutritional goals orally or remain ventilated, feeding should be started preferably through an enteral feeding tube or parenteral nutrition in the rare event that enteral nutrition cannot be established.

Early mobilisation

Mobilisation in the early post-operative period, as recommended for other cardiothoracic surgery is a desirable component of management [73] as it ensures better pulmonary and diaphragmatic function, clearance of secretions, minimises muscle wastage, mobilisation of accumulated fluid and avoids the complications of immobilisation such as DVT and pressure areas. In general, patients are assisted to sit out of bed on the day following surgery, assisted to walk in the next 2 days and generally leave the Intensive Care Unit on day 3-5 as their condition allows.
Anticoagulation and antimicrobial prophylaxis is commenced in the immediate post- operative phase and discussed in detail in the next section along with management of the ambulatory VAD patient.
The guidelines and recommendations above apply to both VAD and TAH, although the medical management of the TAH patient is somewhat simplified as the following factors no longer need to be considered-

- Aortic valve opening
- Presence of VSD
- LV thrombus
- Right heart failure
- Arrhythmias – no ECG monitoring possible
- Use of inotropes
- Global cardiac dysfunction

It is important however to remember in the presence of a TAH or a RVAD, central venous line insertion should be undertaken with extreme caution, preferably under imaging guidance to avoid entrapment of guidewire or lines within the device.

Management of the ambulatory patient on durable MCS

Setting the pump speed

In intensive care

As discussed above, the initial LVAD pump speed is set at a relatively low level.[65] Once the patient is able to be weaned off ventilation, and is haemodynamically stable, the pump speed may be gradually increased. It is important to realise that these patients typically have elevated systemic vascular resistance with low cardiac outputs prior to LVAD and may not require high flows immediately. Most estimates of adequate pump flow are reflected in markers of organ function, rather than dictated by the pump flow estimate provided by the LVAD.
In the early post-operative period, the patient's haemoglobin is typically low and this may also suggest lower than actual pump flows, due to the importance of viscosity on the flow estimation algorithm [74]. While it is generally recommended that the haematocrit setting in the pump is adjusted should the HCT vary by more than 10%, it is our practice to monitor the patient comprehensively and not focus on the pump flow estimate as the primary outcome. It is acknowledged that the flow estimation provided by axial flow pumps is not as accurate as with centrifugal pumps, due to nonlinearity over the operating flow range. [75, 76] As such, the flow trends can be used as a guide, more so than the absolute number. Once the patient is discharged to the ward, the pump speed is not adjusted again, until a formal correlation study of flows and speeds (often called a ramp study, discussed below) is performed prior to going home.

Optimisation of pump speeds Ramp studies

Ramp studies involve a formal gradual increase in pump speed while monitoring pump flows, suction events and non-invasive blood pressure during echocardiography or invasive right heart catheterisation [77]. Often the ramp study during the initial hospitalisation is completed with echocardiography monitoring, and the invasive correlation is used when the patient returns for haemodynamic assessment, usually about 3 months post LVAD implant.
Ramp studies have also been suggested as a marker of adequacy of left ventricular decompression by the LVAD.[77] In the setting of pump thrombosis, an increase in pump speed is not associated with the appropriate decrease in left ventricular volumes or with actual increase in pump flows. However, changes in left ventricular decompression occur late and are indicative of significant impairment of pump function.[78] Pump thrombosis itself may be more easily screened with serum markers of haemolysis due to pump thrombosis, such as serum LDH or plasma free haemoglobin. [79] [80] [81, 82] With the HeartWare HVAD log file system, characteristic patterns in log files can be used to determine onset and treatment outcomes.[83] Power spikes are also associated with pump thrombosis in the HeartMate-II system.[84]

Suction with continuous flow pumps

The main indication and rationale for ramp studies is to determine the maximum safe pump speed that will provide adequate pump output, in the absence of any suction by the pump. As these pumps are continuous flow, there is the possibility of complete chamber decompression at higher pump speeds. We have shown that this is a risk, particularly in the setting of right ventricular impairment– especially early post implantation due to increased pulmonary vascular resistance soon after surgery.[85] Over time, the right ventricular dependency may decrease, although ongoing variation in preload due to dehydration, excessive coughing or Valsalva will continue to place LVAD patients at risk for suction events.

Aortic valve opening

Due to the non-physiological flow through the pump bypassing the aortic valve, the valve may no longer open. This is particularly apparent in the early post-operative phase, and the peripheral pulse is often impalpable. There remains some pulsatility in the pressure due to ventricular contraction contributing to flow pulsatility through the pump even in the absence of aortic valve opening, and it has been suggested to be more prominent in centrifugal compared to axial flow pumps.[76] Most reports, based on echocardiography, suggest that the aortic valve opens in approximately 30-40% of patients. [86-88] The interest lies in the recognition that those patients in whom the aortic valve does not open, have a higher rate of gastrointestinal bleeding, pump thrombosis and other complications.[88] Whether this is an epiphenomenon or causal has not been demonstrated in any study, but has not stopped the suggestion that the pump speed be adjusted down to increase frequency of aortic valve opening and decrease extra-pump complications. Various algorithms have been developed to detect aortic valve opening. [89-92] We have found that preliminary data implementing such algorithms has shown that the aortic valve opening varies throughout the day (Figure 3), as might be expected, and is only marginally related to the valve status taken during supine echocardiography. There has been one prospective study adjusting pump speed according to aortic valve status.[93] This study, examining exercise capacity, demonstrated that decreasing pump speed to encourage aortic valve opening was associated with poorer exercise outcomes.

Exercise

Functional outcomes such as exercise capacity remain an important goal for LVAD patients.[94] One of the important reasons for durable mechanical support is haemodynamic support to allow adequate physical rehabilitation in patients weakened by chronic congestive cardiac failure. It is well recognised that, despite improved cardiac output, LVAD patients only achieve approximately 50% of the age and weight matched predicted exercise capacity (as assessed by cardiopulmonary stress tests, and weight corrected peak oxygen consumption (VO2max). [95] Whether this can be improved by actively adjusting pump speed during exercise has been explored in several studies. [96-99] In general, these have shown that pump flows are able to be successfully augmented, but the increment in exercise capacity is small, if at all. [100] Randomised studies have shown statistically significant, but clinically small, improvements in markers of wall stress (NT-pro-BNP) or invasively measured pulmonary capillary wedge pressures.[96] Augmented speed has not resulted in significant improvement in skeletal muscle blood flow, which remains a major determinant of exercise capacity – discussed below.

Remodelling

The possibility that chronically unloading the LV will assist the heart to recover function is enticing,[101] but again demonstration that increasing pump speed assists in this process has not yet been successful. Changes in genomic regulation have been demonstrated in some, [102] but not all studies.[103] Those most likely to improve are typically younger, non-ischaemic, with shorter duration of heart failure symptoms. [104] Most active remodelling attempts focus on pharmacological strategies in combination with exercise programs, with careful weaning of LVAD therapy and ongoing lifelong monitoring. [104]

Anticoagulation In intensive care

As discussed above, anticoagulation is typically commenced in the ICU. Short acting agents such as heparin are used once bleeding has diminished to an acceptable level (in our unit, less than 50ml/ hour for 4 hours). Once stable, patients are transitioned to long-term vitamin K antagonism and anti-platelet therapy – usually with aspirin. There remains significant variation in regimens across different centres, with some centres advocating dipyridamole, clopidogrel, prasugrel or ticagrelor. [105] While there have been a number of case reports,
[106] at present there is no consensus that warfarin can be substituted with one of the novel oral anticoagulation agents, due to the concern with these agents raised with mechanical heart valves in the RE-ALIGN study, where increased thrombotic and bleeding complications werenoted.[107] Subtherapeutic INR and lack of antiplatelet therapy are risk factors for pump thrombosis.[82]

Monitoring

The target INR for both HeartMate-II and HeartWare HVAD therapy is currently 2.0-3.0. [81, 108]. A lower target had been in use prior to an apparent increase in HeartMate-II pump thrombosis in 2011.[81] This INR window was narrowed in a recent single centre study which examined outcomes following more than 10,000 INR recordings ~ and found that the minimal haemorrhagic or thrombotic events occurred with INR 2.5 – 2.7. [109] While such a narrow window may be difficult to achieve, it is useful to provide a target within the current ‘safe’ recommended working range. As expected, risks of thrombotic complications (mainly cerebrovascular ischaemic events), but also pump thrombotic events increase with INR <2.0, suggesting that bridging anticoagulation with subcutaneous enoxaparin may be appropriate for outpatient management. In the absence of bleeding complications, a supratherapeutic INR may not warrant intervention in view of the risk of overshoot if vitamin K is used.

Antiplatelet therapy

While aspirin is used in >90% of centres, there still remain differences in the recommended dosage. This is likely to be due to institutional experience, as there have not been any trials comparing different aspirin dosages.[105] The commonest dose is 100mg, with some centres using 81mg and some 300mg. In those in whom aspirin is not used due to gastrointestinal symptoms, our practice is to substitute with clopidogrel. Other agents used include dipyridamole, and rarely ticagrelor. While there has been some experience with dual anti-

platelet therapy in addition to oral anticoagulation, recent non-MCS trials suggest excess bleeding, with little improvement in thrombotic events. [110]

Acquired von Willebrand deficiency

Due to the continuous high rotational speed of the impellers in both axial [111] and centrifugal flow [112] pumps, there is uniform disruption of von Willebrand factor (vWF) protein. [113] As vWF is one of the largest circulating serum proteins, and is structured in a manner to ensure that it has large available surface area to ensure rapid binding to disrupted endothelial surfaces, it is particularly susceptible to disruption. It has been suggested that there may be other mechanisms involved in vWF disruption including the down-regulation of ADAMTS-13, the enzyme involved in normal vWF degradation. [113] While in vitro studies suggest inhibition of ADAMTS-13 by doxycycline is successful in improving vWF - collagen binding activity ratio, [114] formal results from a prospective trial of doxycycline on clinical outcomes is awaited. The combination of dual anti-thrombotic therapy (anticoagulation and anti-platelet therapy) with LVAD related vWF disruption both would be expected to increase bleeding in LVAD patients. Gastrointestinal bleeding, cerebrovascular haemorrhage and excess bleeding with non-cardiac surgery have all been well described.

Blood Pressure

While LVAD patients are characteristically hypotensive prior to pump implantation, due to poor cardiac output, within 3 months up to 75% of patients require active therapy to manage hypertension.[115] One of the initial obstacles to blood pressure management however, is measurement. Due to the lack of pulsatility in pressure, conventional Korotkoff techniques may only be successful in 15% of patients by auscultation and only 3% by palpation.[116] Those in greatest need, typically have lower pulsatility, and lower success rates for blood pressure measurement.

Measurement techniques in intensive care

While in intensive care, the standard pressure monitoring is with an intra-arterial pressure line. There is often still some pulsatility in the pressure tracing due to ventricular contraction transiently increasing ventriculo-aortic gradient across the pump, and the pressure waveform may still be slightly pulsatile even without the aortic valve opening. The degree of pulsatility is related to the combination of the effects of ventricular contractility and systemic vascular resistance. A flat arterial line trace suggests either very poor left ventricular contractility, often seen immediately post implant, or excessive pump speed relative to available preload.[65]

As outpatient

The most commonly used method for blood pressure measurement in outpatients, is the combination of sphygmomanometric cuff occlusion with Doppler detection of return of flow through the brachial artery at the level of the antecubital fossa. [65] Successful measurement rates for this technique are usually around 95%.[116] Whether this value obtained is equivalent to the systolic or mean arterial pressure has been controversial. Automated BP cuffs, have limited success, [116] with the most successful machine no longer clinically available.[117]

Alternate means for blood pressure measurement have been suggested, including pulse oximetry waveform detection,[118] and finger-cuff plethysmography.[119]

Outcomes

The importance of BP control has come into focus recently with strong evidence demonstrating adverse outcomes with elevated Doppler-measured blood pressures. [115, 120, 121] In the large HVAD bridge to transplant trial and continued access program, subjects from centres with strict BP management guidelines and criteria had better outcomes than those without active BP treatment.[122] Similarly, a large prospective outpatient study demonstrated increased intracerebral haemorrhage, stroke, aortic regurgitation and pump thrombosis in patients with measured BP above than 85mmHg compared to those below.
[121] There appeared to be a continuum of risk with those with the lowest BP (<80mmHg) at much lower risk than those with average BP >90mmHg. The choice of anti-hypertensive therapy has not yet been defined, and most units use similar agents to those that the patients were taking before LVAD – ACE inhibitors, b-blockers, and diuretics.[115] There is further experience with short acting vasodilator agents such as hydralazine.

General Care

Driveline management

The commonest adverse outcome for chronic durable MCS support is driveline infection (DLI)[123], increasing with duration of support. While this may not be immediately life-threatening or severe, DLI places a significant burden on patients and carers alike and indicate an adverse outcome with prolonged hospitalisation and a trend to increased mortality.[124] Once a DLI occurs, the formation of a biofilm makes it very difficult for it to be fully cleared.

Dressings

Current practice requires VAD driveline exit site dressings to be changed daily, if the dressing is not intact, or if there is evidence of moisture, blood or exudate under the VAD dressing. [125] To minimise driveline movement, and to encourage incorporation of the driveline granulation tissue, the driveline is secured adjacent to the exit site. The driveline securement device (e.g. GRIP-LOK®) should be changed every 3-5 days. Patients are educated concerning driveline care and are individually responsible for their driveline site. The treating team should minimise interaction with the exposed driveline to limit cross contamination. Using a basic dressing pack, standard hand hygiene and non-sterile gloves the dressing covering is removed. Using a circular motion from inside to the outer aspect of the exit site area, repeating 3 – 6 times.[65] At our centre, we use Medihoney, and dress with a split Primapore, overlapping the edges.

Antibiotics

Prior to implantation, prophylactic antibiotics are recommended for a short period. [125] In the absence of consensus, our practice at St Vincent's Hospital (Sydney, Australia), is combination anti-fungal, anti-staphylococcal and anti-pseudomonal agents. One hour prior to implant IV

Fluconazole 800mg over 4 hours; IV Vancomycin 15mg/kg (maximum 1500mg) at and IV Ciprofloxacin 400mg over 1 hour. In the anaesthetic bay, within 60 minutes of surgery commencement, IV Cephazolin 2g is given q4 hours. Post-operatively IV Cephazolin 2g is given every 8 hours for 2 doses and one further IV Fluconazole 400mg dose.
Antibiotics are not routinely prescribed for driveline management, unless there is evidence of an exudate with microbiological confirmation of a pathogenic organism. Once patients have required treatment for DLI, it is our practice to maintain chronic suppressive oral therapy until transplantation, checking organism sensitivities intermittently, under the guidance of infectious disease specialists. The commonest organisms include Staphylococci, and Pseudomonas aeruginosa.[124] Demonstration of positive blood culture mandates 6 weeks of intravenous therapy (often as an outpatient) with indefinite suppressive oral therapy thereafter until transplantation. One of the major considerations for active bloodstream infections, is the association with increased pump-related events, including gastrointestinal bleeding,[126] and cerebrovascular accidents.[127]

Antibiotic prophylaxis post discharge

It is recommended that all patients with LVADs have appropriate dental prophylaxis with either Amoxicillin or Clindamycin as appropriate one hour prior to procedure. [125] While this has not been proven, the higher rate of streptococci (especially viridans Streptococci) in LVAD patients suggests this is reasonable. As with dental work, non-cardiac surgical procedures warrant appropriate prophylactic antibiotics, according to the procedure undertaken.

Exercise therapy

Rehabilitation

Most patients implanted with LVADs require and benefit from a formal rehabilitation exercise program. [128, 129] This is related to most patients, in our centre, being implanted from INTERMACS classification 1 or 2. By definition, these patients are failing medical therapy, and often in incipient multi-organ distress. We, and others, have found that pre- implantation frailty contributes significantly to adverse outcomes. [130]. Focussed rehabilitation and strengthening to allow patients to care for their LVAD and activities of daily living improves quality of life and minimises rehospitalisation. [128]

Exercise capacity

Exercise therapy, independent of rehabilitation pre-discharge has been shown to improve outcomes.[131] The nature of exercise – high intensity vs. low intensity is actively under study at present. Patients are generally encouraged to maintain regular walking and to regain strength, in preparation for subsequent transplantation. While measured peak oxygen utilisation does not return to normal with LVAD implant, the quality of life, and distance walked in 6 minutes have been shown to improve. [132, 133] The disconnect between cardiopulmonary stress testing and functional outcomes is surprising, although even with intermittent speed augmentation, achieved exercise cardiac output with LVAD therapy, or even transplantation, remains only a fraction of that of the normal heart. [134]

Activities of daily life

Showering

While patients do have limitations placed on their activities, including avoiding water sports and swimming, all patients are encouraged to shower as soon as they are physically able. Waterproof bags protect the controller and batteries. Careful drying and cleaning of the driveline site takes place after showering.

Travelling

Due to distances between implanting sites and home, patients often need to undertake air travel. All patients are given an information sheet outlining the type of device, and need to take batteries as well as spare controller on-board. The HVAD pump device and controlled have been FAA approved.

Driving

As of 2016, approval for conditional licence for non-commercial (private) driving has been given by the Roads and Maritime Services in Australia.[135] Approvals vary across countries and even between states in the USA. Patients must be assessed individually by the implanting centre and be medically stable at least 3 months post-LVAD implantation. The main rationale for this is the fact that, even in the setting of ventricular arrhythmia, patients often maintain consciousness and control with LVAD support, independent of the cardiac rhythm.[136] Patients with dual LVAD and RVAD are currently excluded. Commercial driving remains excluded.

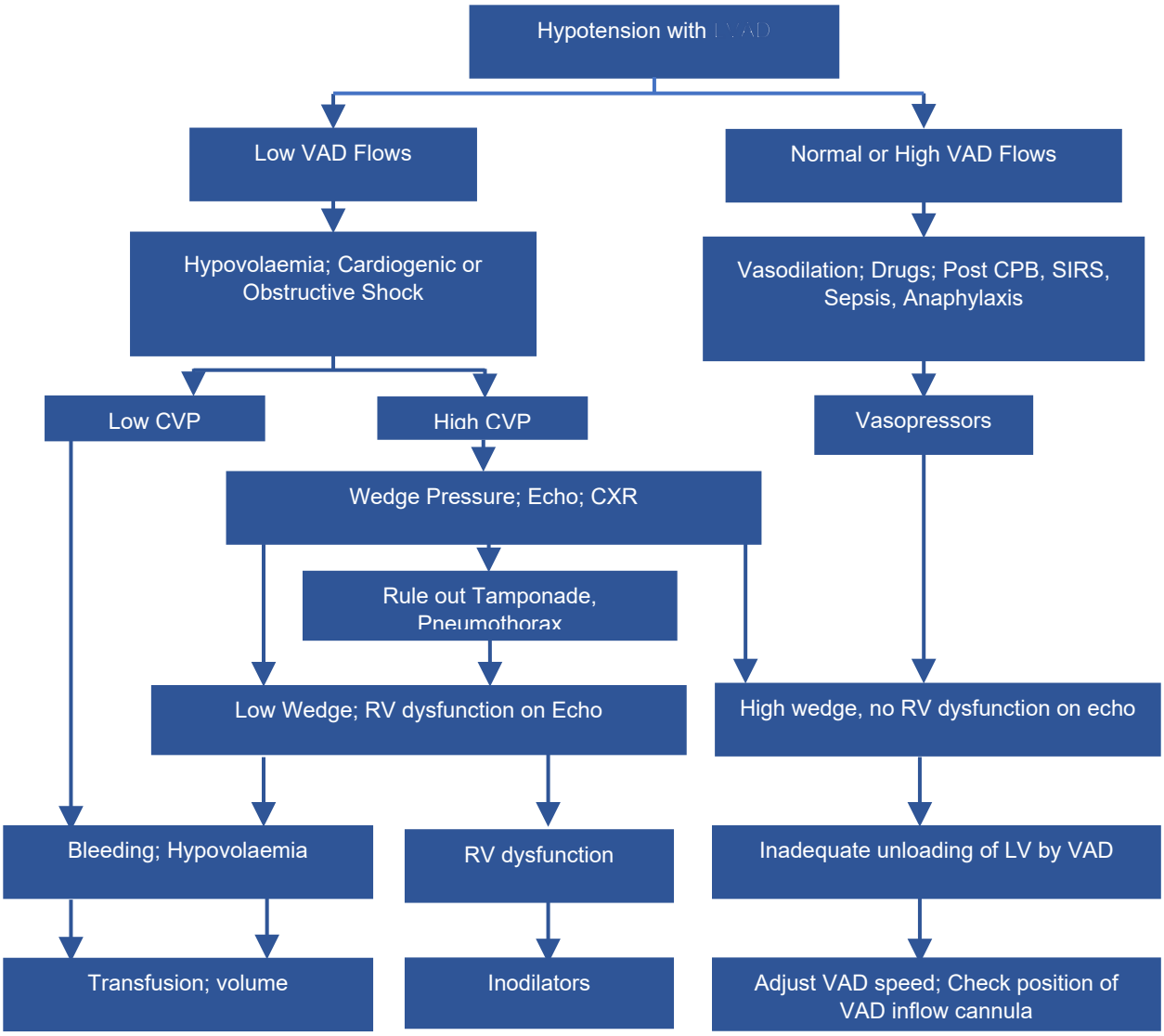
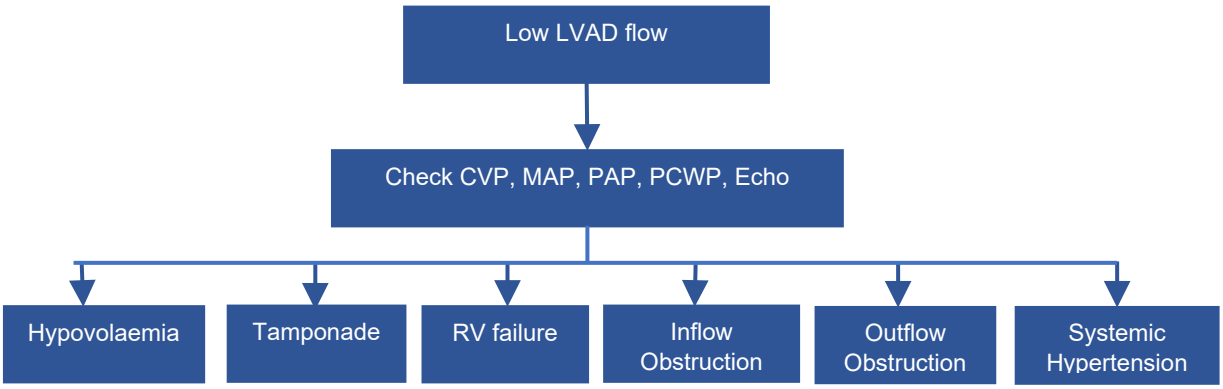


Figure 1. Troubleshooting algorithm for systemic hypotension with continuous flow Left Ventricular Assist Device (LVAD) in the peri-operative period. (modified from [125]) CPB - cardiopulmonary bypass, SIRS - Systemic Inflammatory Response Syndrome, CVP - Central Venous Pressure, LV - left ventricle, RV - right ventricle



CVP	Low	High	High	High	High	High
PAP	Low	Low	High/N	High	High	High
PCWP	Low	Low	Low	High	High	High
MAP	Low	Low	Low	Low	Low	High
Echo	Underfilled	RV compression	Dilated RV	LV dilated AV opening Inflow malposition	LV dilated AV opening	LV dilated

Figure 2. Troubleshooting algorithm for low flows with continuous flow Left Ventricular Assist Device (VAD) in the peri-operative period [VAD Inflow and Outflow obstruction are rare causes ((modified from [125]). CVP - Central Venous Pressure, MAP - Mean Arterial Pressure, PAP - Pulmonary Artery Pressure, PCWP - Pulmonary Capillary Wedge Pressure, Echo - Echocardiography RV - Right Ventricle, LV - Left Ventricle, AV - Aortic Valve

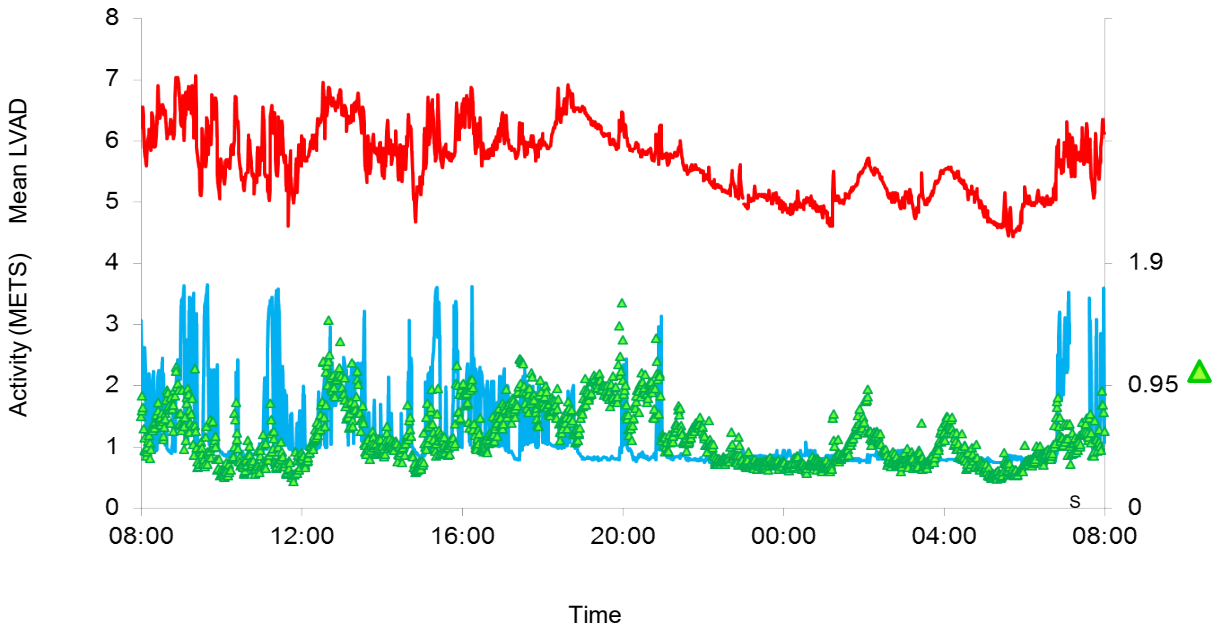


Figure 3. 24-hour variation in LVAD flow according to activity. The aortic valve opening is determined as described in Hayward et al (93).

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ICU INFUSIONS

ADRENALINE
2mg in 100 mls 5% Dextrose

NORADRENALINE
4mg (2 ampoules) in 100 mls 5% Dextrose

DOBUTAMINE
250mg in 100mls 5% Dextrose

ISOPRENALINE
2mg in 500 mls 5% Dextrose

GLYCERYL TRINITRATE
50mg in 100 mls 5% Dextrose

SODIUM NITROPRUSSIDE
50mg in 250 mls 5% Dextrose

MILRINONE
10mg in 100mls 5% Dextrose

ESMOLOL
2.5g in 250 mls 5% Dextrose

VASOPRESSIN
20 units in 100 mls 5% Dextrose

LIGNOCAINE
4gm in 500 mls 5% Dextrose

AMIODARONE
900mg in 100 mls 5% Dextrose

T3
40 mg in 100 mls 5% Dextrose.

SECTION VII TRANSPLANT DRUGS

IMMUNOSUPPRESSIVE AGENTS

i. **TACROLIMUS**
ii. **MYCOPHENOLATE MOFETIL (Cellcept)**
iii. **METHYL PREDNISOLONE**
iv. **SIROLOMUS/EVEROLIMUS**
v. **BASILIXIMAB**

OTHER DRUGS

i. **GANCICLOVIR**

TACROLIMUS FK506, Prograf

USES
Tacrolimus is used for the prevention of rejection of allografts of solid organs. In cardiopulmonary transplantation, it is used in conjunction with corticosteroids and mycophenolate or azathioprine.

MECHANISM OF ACTION
Tacrolimus suppresses T cell activation and T helper cell dependent B cell proliferation, as well as the formation of lymphokines such as interleukins-2 and 3 and gamma-interferon and the expression of the interleukin-2 receptor.

CAUTIONS
Neurological and CNS disorders have been reported with Tacrolimus therapy. Patients experiencing such events should be carefully monitored. In cases of severe or worsening neurological disorder, adjustment of the immunosuppressive regimen should be considered.
Patients with renal impairment: No dose adjustment is required. However, careful monitoring of renal function is recommended
Impaired hepatic function: Tacrolimus is extensively metabolised by the liver. In patients with hepatic impairment, dose reduction is recommended.
The principal adverse reactions of Tacrolimus are tremor, headache, diarrhoea, hypertension, nausea, and renal dysfunction. These occur with oral and intravenous administration of Tacrolimus and may respond to a reduction in dosing. Diarrhoea is sometimes associated with other gastrointestinal complaints such as nausea and vomiting.

Hyperkalaemia, hypomagnesaemia and hyperuricaemia have occurred in patients receiving Tacrolimus therapy. Hyperglycaemia has been noted in many patients; some may require insulin therapy.

Allergic and anaphylactoid reactions have been observed in patients receiving tacrolimus.

DRUG INTERACTIONS

When considering co administration of Tacrolimus with other drugs the potential for exacerbation of toxic effects should be carefully considered. Care should be taken when using compounds known to have nephrotoxic effects, such as aminoglycosides, amphotericin, cotrimoxazole, gyrase inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs) and vancomycin. When Tacrolimus is administered together with potentially neurotoxic substances such as ganciclovir or acyclovir, the neurotoxicity of these drugs may be enhanced. Tacrolimus has been shown to increase phenytoin blood levels. Hyperkalaemia has been reported in some patients receiving Tacrolimus. Where there is a risk of Hyperkalaemia, potassium sparing diuretics should be avoided. Care should also be taken when administering potassium supplements or other agents known to increase serum potassium levels.

During treatment with Tacrolimus, vaccinations may be less effective and the use of live attenuated vaccines should be avoided.

Tacrolimus is extensively metabolised via the hepatic microsomal cytochrome P450 enzyme system. Since tacrolimus is metabolised mainly by P450 3A4 enzymes, substances known to inhibit these enzymes may decrease the metabolism of tacrolimus with resultant increases in whole blood or plasma levels. Drugs known to induce these enzymes may result in an increased metabolism of tacrolimus and decreased whole blood or plasma levels. Tacrolimus may have an inducing or inhibitory effect on these enzymes and care should be taken when coadministering other drugs known to be metabolised by the cytochrome P450 enzyme system.

DRUGS REPORTED TO INCREASE TACROLIMUS BLOOD LEVELS

Macrolides	Erythromycin, Roxithromycin, Clarithromycin
Azole Antifungals	Ketoconazole, Fluconazole, Itraconazole, Voriconazole
Calcium Antagonists	Diltiazem, Verapamil
Other	High dose Methylprednisolone (>250mg), Metoclopramide, Acetazolamide, Colchicine? Norfloxacin, ?Cimetidine, ?Imipenem

DRUGS REPORTED TO DECREASE TACROLIMUS BLOOD LEVELS
Phenytoin, Carbamazepine, Barbiturates, Rifampicin, Octreotide, Cotrimoxazole (high dose)

ADMINISTRATION
It is recommended that the oral daily dose be taken in two divided doses. The capsules should be swallowed with fluid, preferably water. The capsules should be taken on an empty stomach or at least one hour before a meal to achieve maximal absorption
Prograf Concentrated Injection should be diluted in glucose 5% solution in polyethylene or glass bottles or in sodium chloride 0.9% injection solution in polyethylene bottles. The concentration of a solution for final infusion produced in this way should be in the range 0.004 to 0.1 mg/mL. The solution should not be given as a bolus

USUAL DOSAGE
Tacrolimus should only be prescribed by the transplant physician. Dose varies between 0.1 – 10 mg po bd and is adjusted according to blood levels and renal function similar to CYCLOSPORIN. Doses less than 0.5 mg need to be made up by the patient diluting 0.5 mg with 10mls of water and taking the appropriate volume.

MYCOPHENOLATE MOFETIL CellCept®

MECHANISM OF ACTION

Mycophenolate mofetil (MM) is converted to mycophenolic acid (MPA) after oral administration. MPA inhibits the de novo pathway for guanosine nucleotide synthesis by competitively inhibiting inosine monophosphate dehydrogenase. Absorption is unaffected by food. MPA is metabolised in the liver to inactive metabolites, which are mostly renally excreted. It should be used in conjunction with CYCLOSPORIN or tacrolimus and prednisolone.

USES

For prophylaxis of organ rejection and treatment of refractory rejection as an alternative to azathioprine.

CAUTIONS

The main adverse effects reported with mycophenolate are diarrhoea, leucopoenia, infection and vomiting. Gastrointestinal haemorrhage occurs in 3% of patients. Like all immunosuppressants, MM increases the risk of developing lymphomas and other malignancies post-transplant.

PRECAUTIONS

Mycophenolate is considered a hazardous substance therefore nursing staff should wear blue gloves, mask and gown when administering mycophenolate intravenously or via a nasogastric tube.

DRUG INTERACTIONS

Acyclovir - Increased blood levels of both acyclovir and the inactive metabolite of MPA has been reported.

Antacids (containing magnesium and aluminium e.g., Mylanta® and Simeco®) and cholestyramine - bind mycophenolate in the gut and reduce absorption. If cholestyramine necessary, give at least 6 hours before or 2 hours after mycophenolate. Separate antacids by two hours from mycophenolate

No interaction has been observed between Mycophenolate and the following drugs: CYCLOSPORIN, ganciclovir, oral contraceptives (norethisterone 1mg / ethinyloestradiol 35µg - single dose study only), trimethoprim/sulphamethoxazole (Bactrim DS® / Septrim Forte® / Resprim Forte®).

Administer magnesium supplements (Magmin®) at least 2 hours apart from mycophenolate.

DOSAGE IN RENAL IMPAIRMENT

Reduced dosage is required only in severe chronic renal impairment. i.e., GFR < 25mL/min. NOT removed with haemodialysis.

ADMINISTRATION

Mycophenolate is administered twice daily Oral dosing:

Usual dosage is 1.0-1.5g twice daily.

Nasogastric administration

Wear cytotoxic Personal Protective Equipment (blue gloves, mask and gown) Use 500mg tablets

Place tablets into the barrel of a 50mL syringe and draw up 20mL Glucose 5% into syringe. Cap syringe and shake well until tablets dissolved to form a suspension. (They may take about10-15 minutes to dissolve)
Give via NG with flush of dextrose. Warning: Avoid inhalation or direct contact.
Intravenous Administration
Wear cytotoxic Personal Protective Equipment (blue gloves, mask and gown). Intravenous dose is the same as the oral dose.

Reconstitute and infuse with 5 % Glucose only. Mycophenolate is incompatible with 0.9% Sodium Chloride and Hartmanns.

Reconstitute each 500mg vial with 14mL 5% Glucose Dilute dose to 250mL with 5% Glucose Infuse over 2 hours via a central line

CAUTION
NEVER administer by bolus injection.
Administration by a peripheral line causes phlebitis and thrombosis.

STORAGE
Unopened vials are stored at room temperature.
Reconstituted drug should be used immediately but may be stored for up to 4 hours at 15-30□C if needed.

THERAPEUTIC DRUG MONITORING
Mycophenolate target trough (12-hour post dose) level is 2-5mg/L (CeMyLungs).

METHYLPREDNISOLONE Solumedrol® 6- -Methylprednisolone

MECHANISM OF ACTION
Methylprednisolone is a synthetic glucocorticoid, used principally as an anti-inflammatory agent or immunosuppressant. It has minimal mineralocorticoid properties. Suppression of the immune response occurs via reducing the activity and volume of the lymphatic system, producing lymphopoenia, reducing immune-globulin and complement concentrations and possibly depressing reactivity of tissues to antigen-antibody interactions. It inhibits lymphocyte activation by inhibiting secretion of IL-1 by activated monoctytes and macrophages.
USES
Methylprednisolone is used as part of immunosuppressive therapy to prevent or treat rejection in transplant recipients.

CAUTIONS
Glucocorticoids used in pharmacological doses have many adverse effects, particularly when these agents are used for extended periods. For a more detailed explanation of the side-effects of steroid therapy, refer to the appropriate pharmacological texts. Some of the effects are listed here:
- Adrenocortical insufficiency - Reduced glucose tolerance
- Muscle wasting - Increased appetite

- Delayed wound healing - Pancreatitis
- Osteoporosis - Ulcerative oesophagitis
- Increased susceptibility to infections - Peptic ulceration
- Sodium retention and potassium loss - Increased intraoccular pressure
- Cataracts - Headache, insomnia, restlessness
- Vertigo, mental disturbances - Skin atrophy, easy bruising, acne
- Hirsutism - Cushingoid state
- Hypercholesterolaemia and atherosclerosis - Avascular necrosis of the femoral head

DRUG INTERACTIONS
Barbiturates, phenytoin and rifampicin induce hepatic metabolism of prednisolone. Oestrogens may enhance effects of methylprednisolone. NSAIDs may increase the risk of GI ulceration. Potassium depleting drugs may enhance the potassium wasting effects of prednisolone.

Ketoconozole inhibits the metabolic clearance of methylprednisolone and dose reductions may be required.

ADMINISTRATION
Methylprednisolone is used as an intravenous glucocorticoid for treatment of rejection episodes, or when oral glucocorticoid therapy is not possible.
Intravenous methylprednisolone is given as the sodium succinate salt (Solu-Medrol). Doses of 500mg or more are usually infused over 30-60 minutes after dilution with normal saline or 5% dextrose.
Smaller doses may be given as a slow IV push over 1-2 minutes.

USUAL DOSAGE
For treatment of rejection episodes, methylprednisolone is given at 500mg - 1 gm daily for 3 days. As a substitute for oral prednisolone, 4mg of methylprednisolone is equivalent to 5 mg of prednisolone.

SIROLIMUS Rapamycin Rapamune

USES
Selective immunosuppressant used for the prevention of rejection of allografts of solid organs

MECHANISM OF ACTION
Sirolimus inhibits T cell activation induced by most stimuli by blocking calcium dependent and calcium independent intracellular signal transduction. Studies demonstrated that its effects are mediated by a mechanism that is different from that of CYCLOSPORIN, tacrolimus and other immunosuppressive agents.

CAUTIONS
Hepatic impairment In mild and moderate hepatically impaired patients (Child-Pugh classification of A or B), t1/2 was increased 43%
The effect of renal impairment on the pharmacokinetics of Sirolimus is not known. However, there is minimal (2.2%) renal excretion of the drug or its metabolites. Renal function should be

monitored during concomitant administration of Rapamune and CYCLOSPORIN. Appropriate adjustment of the immunosuppression regimen should be considered in patients with elevated serum creatinine levels. Caution should be exercised when coadministering other agents that are known to have a deleterious effect on renal function.

Body as a whole lymphocele, peripheral oedema, abnormal healing, infections (such as Mycobacterial infections, Epstein-Barr virus, CMV and herpes zoster); herpes simplex; sepsis.

Cardiac disorders: tachycardia.

Gastrointestinal disorders: Abdominal pain, diarrhoea, stomatitis, pancreatitis.

Blood and the lymphatic system disorders: Anaemia; thrombocytopenia, leucopenia; thrombotic thrombocytopenic purpura/ haemolytic uraemia syndrome.

Metabolism and nutrition disorders: Hypercholesterolaemia, hypertriglyceridemia, hypokalaemia; increased lactate dehydrogenase (LDH), increased AST, ALT.

Musculoskeletal, connective tissue and bone disorders: Arthralgia, bone necrosis.
Respiratory, thoracic and mediastinal disorders: Epistaxis; pneumonia; pneumonitis. Skin and subcutaneous tissue disorders: Acne, rash.

DRUG INTERACTIONS
Sirolimus is extensively metabolised by the CYP3A4 isozyme in the intestinal wall and liver. Sirolimus is also a substrate for the multidrug efflux pump, P-glycoprotein (P-gp), located in the small intestine. Therefore, absorption and the subsequent elimination of systemically absorbed Sirolimus may be influenced by substances that affect these proteins.

DRUGS REPORTED TO INCREASE SIROLOMUS BLOOD LEVELS
CYCLOSPORIN
Macrolides antibiotics Erythromycin, Roxithromycin, Clarithromycin Azole Antifungals Ketoconazole, Fluconazole, Itraconazole Calcium Antagonists, Diltiazem, Verapamil
Prokinetic agents Cisapride, metoclopramide

DRUGS REPORTED TO DECREASE SIROLOMUS BLOOD LEVELS
Antibiotics Rifampicin
Anticonvulsants Phenytoin, carbamazepine, barbiturates

ADMINISTRATION
The dosing syringe should be used to withdraw the prescribed amount of Sirolimus oral solution from the bottle. Empty the correct amount of oral Sirolimus solution from the syringe into a glass container with at least 60 mls of water or orange juice. Do not empty the Rapamune oral solution into a plastic, paper or polystyrene cup. Do not use any liquids other than water or orange juice for dilution. Stir vigorously and drink at once. When mixed with water or orange juice, Sirolimus oral solution produces a white to off-white dispersion. Refill the glass container with an additional volume (minimum of 120 mls) of water or orange juice, stir vigorously, and drink at once. Grapefruit juice must not be taken with Sirolimus

To minimise the pharmacokinetic effect of CYCLOSPORIN (microemulsion) on Sirolimus, administration of Sirolimus and CYCLOSPORIN (microemulsion) should be separated by approximately four hours.
Oral solution, 1 mg/mL

Rapamune oral solution may be kept at room temperature (up to 250C) or refrigerated at 2-80C in the dosing syringe for up to 24 hours. After dilution, the preparation should be used immediately.

USUAL DOSAGE
Sirolimus should only be prescribed by the transplant physician. A loading dose of 10mg on the first day well separated from CYCLOSPORIN is given. This is followed by a maintenance dose of 1-2mg per day as a single daily dose around midday. It is adjusted according to levels.

ANTITHYMOCYTE GLOBULIN (equine) ATG, Atgam®

MECHANISM OF ACTION
Antithymocyte globulin (ATG) is immunoglobulin G (IgG) prepared from plasma of healthy horses hyperimmunised with human thymus lymphocytes. It principally inhibits cell-mediated immune responses by elimination of antigen reactive T-Cells in peripheral blood.

USES
ATG is used as part of induction immunosuppression regimens to prevent acute allograft rejection in the immediate postoperative period. It can also be used to treat episodes of steroid-resistant rejection occurring after transplantation (rescue therapy).

CAUTIONS
Fever and chills are the most common adverse effects, but tend to decrease in severity after a few doses. Antipyretics, antihistamines or corticosteroids can generally control these reactions.

Leukopenia and thrombocytopenia also commonly occur. Anaphylaxis occurs in less than 1%, serum sickness may occur within 6-18 days of initiation of therapy. Rarely, cardiac, GI and renal side effects may occur.

ADMINISTRATION
A medical officer must be present when the first dose of ATG is administered. The first dose of ATG is administered at anaesthetic induction by slow IV infusion over a period of 4 hours. Ideally the concentration should not exceed 1mg/ml (max concentration = 4mg/ml). A 0.22-micron MILLEX filter must be used when administering ATG. Invert the infusion bag so the undiluted ATG does not contact the air inside the bag. DO NOT SHAKE TO MIX. See separate administration guidelines.

USUAL DOSAGE
ATG is used in cardiac transplant recipients with a creatinine > 150 Initial dose in anaesthetic bay is ATG 500mg in Normal Saline.

ATG is administered over 5 days post-transplant and titrated according to CD2 count (aim 50-100).

GANCICLOVIR Cymvene®, DHPG, 9-(1, 3-dihydroxy-2-propoxymethyl)-guanine

MECHANISM OF ACTION
Ganciclovir is phosphorylated intracellularly and acts as an inhibitor of viral DNA polymerase, and a false nucleotide base. It thereby inhibits viral DNA chain elongation and/or causes the formation of mutant viral DNA chains, thus inhibiting viral replication.

USES
Ganciclovir is used to prevent or to treat infections due to human cytomegalovirus (CMV). It also has some activity against herpes simplex virus type I and II (HSV-1 and HSV-2), human herpes virus type VI, Epstein-Barr virus (EBV) and varicella-zoster virus (VZV).

CAUTIONS
Adverse effects of ganciclovir are usually dose-dependent, and are therefore more common in patients being treated for CMV infection. Adverse effects include:
- Neutropenia
- Thrombocytopenia
- Retinal Detachment (in patients receiving treatment for CMV retinitis)
- CNS effects (headache, confusion and seizures)
- Abnormal Liver Function Tests
- Nausea and vomiting
- Renal Impairment

DRUG INTERACTIONS
Foscarnet - Additive antiviral effects
Nephrotoxic Drugs - increases the risk of ganciclovir induced nephrotoxicity. Imipenem - Cilastatin - Generalised seizures have occurred.

ADMINISTRATION
Ganciclovir must be infused over one hour. The infusion solution is supplied ready diluted. The dose to be given must be calculated and added to a burette. The drug must be handled as a cytotoxic agent (see SVH Policy and Procedure Manual re handling of Cytotoxic Drugs).

USUAL DOSAGE PROPHYLAXIS
Heart Recipients: In all CMV 'mismatched' heart recipients (i.e., CMV negative recipient receiving CMV positive organ)
- 5mg/kg on Monday, Wednesday and Friday for 6-10 weeks post - TX.
- Prophylaxis may be recommenced during treatment of rejection.

TREATMENT OF CMV INFECTION
Heart Recipients

5mg/kg/q12h for 14-21 days. After 3-5 days of treatment, the dosage may be combined and given once daily to facilitate outpatient treatment. This is an individual decision made by the transplant team according to the patient's condition.

DOSAGE IN RENAL IMPAIRMENT
Doses of ganciclovir must be reduced in renal impairment. The following is a guide:

Creat. Clear. (ml/min/1.73m2)	Dose (mg/kg)	Interval
> 70	5mg/kg	12
50-69	2.5mg/kg	12
25-49	2.5mg/kg	24
10-24	1.25mg/kg	24
< 10	1.25mg/kg	3/wk after haemo