Chapter 11

Mechanical Circulatory Support, Heart Transplantation, and Heart and Lung Transplantation

A. Mechanical Circulatory Support Systems

The Mechanical circulatory supports are used to unload the heart and provide adequate perfusion of the organs in end stage heart failure and / or cardiac dysfunction in a variety of clinical situations for varying lengths of time. The mechanical circulatory support systems comprise of intraaortic balloon pumps, extracorporeal membrane oxygenation (ECMO) with centrifugal pump circuits, and ventricular assist devices (VADs).

Intraaortic balloon pumps are used in refractory low cardiac output states in children after open heart surgery and may result in > 50% long-term survival.

Extracorporeal membrane oxygenation (ECMO) with centrifugal pump circuit is a common support system and offers biventricular and pulmonary support. This support is widely used in children, particularly in small infants after cardiac operations and in severe respiratory failure. This mode of support is only suitable for a short term application.

Ventricular assist devices (VADs) are used for a long term support of the left ventricle or both the right and left ventricle, and allow patients full mobilization.

11.1 Intraaortic Balloon Pump (IABP)

11.1.1 Principles

There is a common misconception that increased elasticity of the aorta in children prevents effective augmentation. The IABP usage, therefore, in young children is very rare.

Effective counterpulsation is achievable in the highly elastic aorta of young children.

Children with ↓ cardiac output states are likely to have an associated right ventricular (RV) failure and pulmonary problems.

In children with congenital heart disease with severe left ventricular (LV) failure, poor RV and pulmonary function are not supportable with IABP.

IABP and left ventricular assist devices (LVAD) are limited to supporting the left ventricle.

In refractory low cardiac output states in children ECMO is a common mode of support because it offers biventricular and pulmonary support.

11.1.2 Physiologic Effects of IABP

Unloads the ventricle in the ejection phase of the cardiac cycle by balloon deflation. Myocardial blood flow ↑ during the filling phase by diastolic augmentation (by balloon inflation).

Net results: ↑ myocardial oxygen supply, ↓ myocardial oxygen demand.

Increases endocardial viability ratio (EVR).

Promotes myocardial recovery from ischemic injury.

IABP allows reduction of doses of inotropic drugs quickly.

11.1.3 Indications for IABP

1) Patients with severe preoperative ventricular dysfunction.

2) Patients that cannot be weaned from CPB. The cardiac failure is due to a prolonged surgery with extended cross-clamp times or preoperative ventricular dysfunction.

3) Patients with sudden deterioration in ICU after a good surgical repair.

4) Progressive deterioration of ventricular function in ICU.

Note: (adrenaline at doses > 0.5 μg/kg/min is a strong indication for initiating IABP and with a Fontan procedure, use of even a low dose of adrenaline may prompt IABP use.)

Fontan procedure and IABP:

The incidence of failure to retrieve poor ventricular function after the Fontan procedure is high. In a failure after Fontan, in addition to ventricular failure, exhaustive search is done for residual obstruction or other defects. IABP, post Fontan reduces pulmonary vascular resistance by ↓ afterload, decreases end-diastolic and filling pressures, and ↑ myocardial oxygen supply.

Survival for children requiring IABP therapy post Fontan is only 10-11%, but the overall survival rate of children weaned from balloon is 50 to 71%.

Note:

1) IABP indication due to failure to wean from CPB is not an ideal indication for use of ECMO or LVAD. IABP is not a substitute for ECMO or LVAD.

2) Use of IABP before need for ECMO or LVAD arises, it prevents ventricular deterioration.

3) Start IABP use, well before ventricular function is not capable of sustaining the cardiac output.

11.1.4 Technique of IABP Operation

i) Selection of a balloon catheter:

Follow Datascope guidelines based on the age and weight for the selection of an appropriate catheter. Pediatric catheter is smaller, contains no pressure monitoring lumen, and is not pre-wrapped. In general, a balloon that approximates 50% of a normal predicted stroke volume for each patient is appropriate. The balloon size may be smaller than recommended because of small femoral artery size. Larger patient (> 50 kg) may receive 34-cc 'adult' balloon.

ii) Site of balloon insertion:

A. Smaller infants (median weight 4.5 kg):

Utilize the purse-stringed cardioplegia delivery site and insert directly via the ascending aorta. The chest was left open and the wounds are covered with a silicone membrane sutured to the skin.

B. Larger infants (median weight > 5 kg):

Direct cut down to the artery, and insert balloon directly via the common femoral artery or via a 5-mm Gore-Tex sleeve, anastomosed end to side to the femoral artery.

Verify the balloon position in all techniques by a roentgenogram.

iii) Pumping console:

The Datascope System 97 or 90 pumping console with a pediatric volume-limiting chamber is employed. Do manual filling of the catheter balloon with helium hourly. Do manual adjustment for augmentation timing for any changes in heart rate > 10 beats/min to ensure optimal diastolic augmentation and presystolic dip.

iv) Balloon pump deployment and timing:

Once IABP is deployed, the arterial monitoring is transferred to the IABP console and the tasks below are undertaken.

a) Monitor the following:

Femoral arterial, central venous and left atrial pressures, systemic arterial oxygen saturation, electrocardiogram, and core and skin temperatures.

b) Heparin infusion:

Administer heparin while the patient is on the balloon pump.

Adjust the heparin dose to keep (APTT) 1.5 to 2 times the normal value.

c) Timing of balloon: See Figure 30, 31 and 32 and the discussion in the following pages.

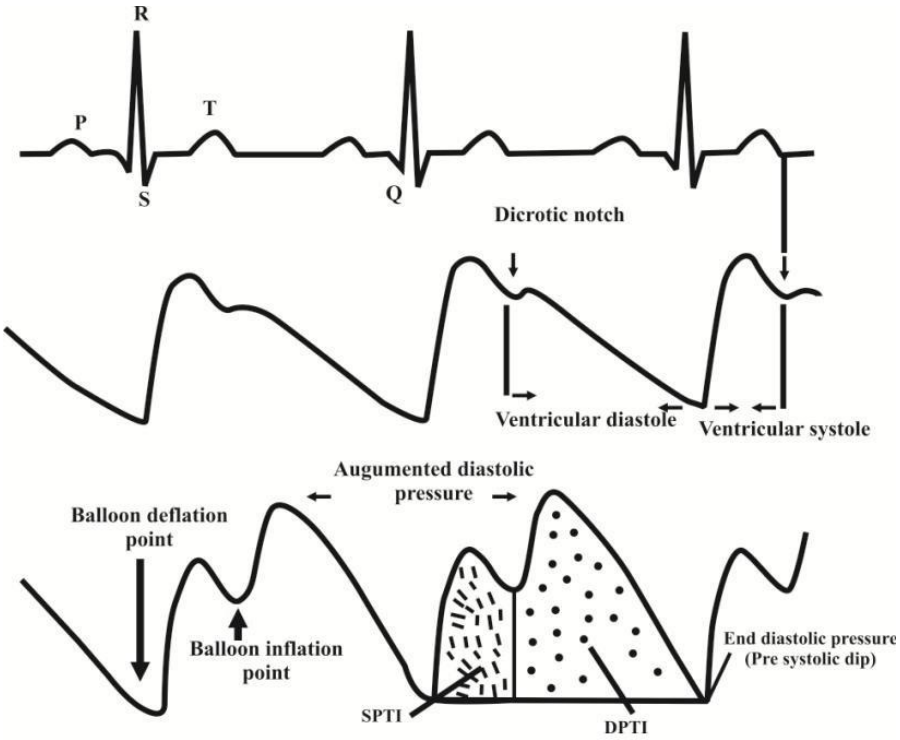

Figure 30 *Timing (Inflation and deflation) of intra-aortic balloon pump: Top strip: QRS complex on EKG represents myocardial depolarization. ST segment and T wave on EKG represents myocardial repolarization and coincides with ventricular systole. Ventricular diastole corresponds to TP interval on EKG. Middle and Lower strips: Arterial pressure tracing with and without balloon pump assistance: Normal arerial pressure tracing showing dicrotic notch and relation ship to ventricular systole and ventricular diastole. Balloon inflation point at the beginning of diastole corresponds to dicrotic notch on arterial tracing and end of T wave on EKG. Balloon deflation corresponds to the beginning of systole or beginning of ST segment on EKG. SPTI = systolic pressure time index, DPTI = diastolic pressure time index.*

Inflate the balloon at the beginning of ventricular diastole which corresponds to end of T wave on EKG / or dicrotic notch on arterial tracing.

Deflate the balloon at the beginning of ventricular systole which corresponds to the beginning of ST segment on EKG.

The balloon is normally operated on “EKG collapse mode” which indicates that the balloon is operated in an inflated mode with regular balloon deflation triggered by R wave on EKG. This mechanism can be disabled by the operator and can be turned on to a “pressure mode” which indicates that the balloon console (as in Datascope) senses arterial pressure tracing for proper timing of balloon deflation and inflation.

The systolic pressure time index (SPTI) represents the area under arterial pressure tracing in ventricular systole. It is decreased by the assistance of a balloon pump due to decreased end-diastolic pressure (pre-systolic dip) and decrease in systolic pressure. Systolic pressure time index correlates with myocardial oxygen demand. The diastolic pressure time index (DPTI) represents the area under arterial pressure tracing in ventricular diastole. It is increased by the assistance of a balloon pump due to augmented diastolic pressure (suprasystolic diastolic argumentation). Diastolic pressure time index correlates with myocardial oxygen supply.

The arterial wave forms of a patient assisted with IABP are shown in figures 31 and 32. Balloon assistance increases the diastolic pressure, as well decreases systolic and aortic end-diastolic pressure or presystolic dip. Suprasystolic diastolic augmentation (or pressure increase) is not often achieved in patients under 2 years of age, even after maximum balloon augmentation.

Physiologic changes invoked by counter pulsation: a) Increase in the diastolic pressure-time index (DPTI) which ↑ myocardial oxygen supply. b) Decrease in the tension-time index which ↓ myocardial oxygen demand (see Figure 30). c) Increase in enocardial viability ratio (EVR), and promotes recovery from myocardial ischemia.

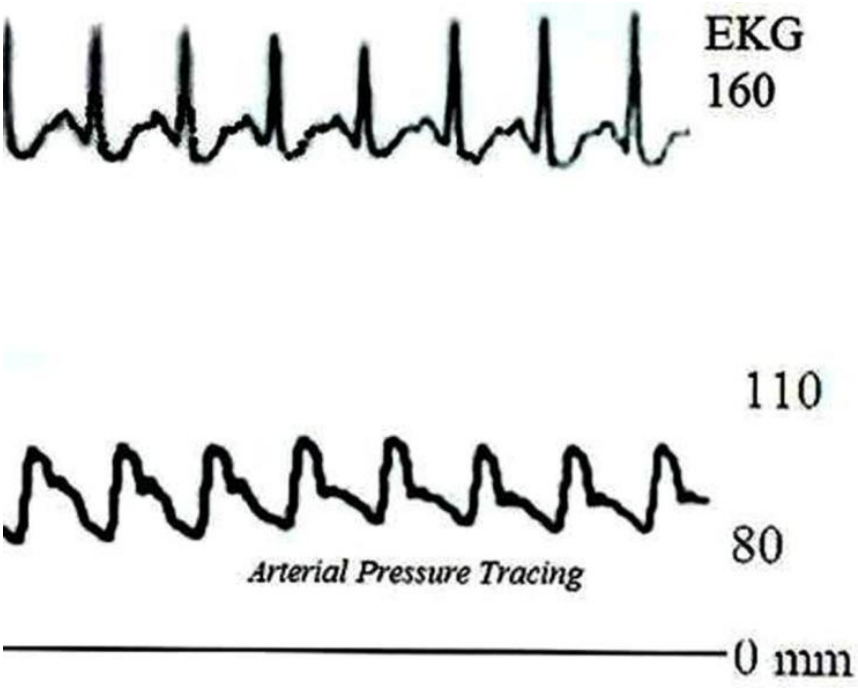

Figure 31 *Arterial wave form at the start of IABP counter-pulsation as augmentation is reduced from maximum (left) to minimum (right). Most likely it is due to a gas loss in a balloon catheter. Even at maximum augmentation, suprasystolic augmentation is not achieved. This is frequently seen in patients less than 2 years of age. Suprasystolic augmentation could often be achieved by induced peripheral vasoconstriction (i.e., active cooling to a core temperature of 34 ℃ and to suppress tachycardia above 200 beats/min).*

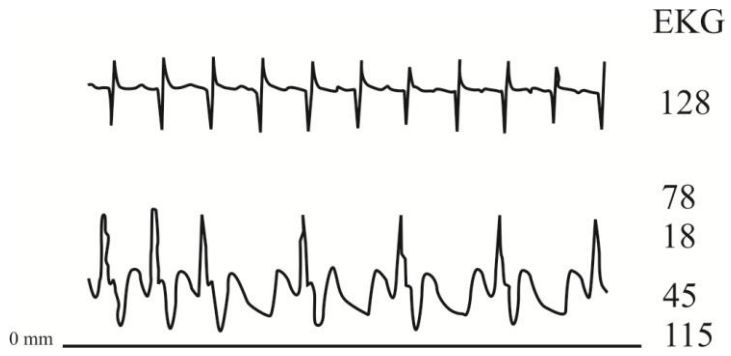

Figure 32 *Arterial wave form of a patient with IABP in 1:1 (left) and 1:2 (right) frequency. Suprasystolic diastolic augmentation is achieved as well as a lowered aortic end-diastolic pressure or presystolic dip.*

11.1.5 Weaning from IABP

a) Criteria to begin weaning from the IABP:

i) Hemodynamic stability with signs of good cardiac output.

ii) Reduced inotropic requirement, usually milrinone and/or dobutamine at 5 μg/kg/min.

iii) Normal BP for age, normal CVP, and LAP < 10 mm Hg.

iv) Improved myocardial contractility on echocardiography.

v) Satisfactory urine output (greater than 2 mL/kg/hr).

vi) Central/peripheral temperature gradient is not more than 2 ℃.

vii) No metabolic acidosis.

b) Procedure of weaning:

1. Augmentation is reduced to 50% by pressing the augmentation reduction button every 5 minutes, until the visual indicator on the console corresponded to 50% reduction.

2. If 50% reduction is tolerated for 4-6 hours, ↓ balloon frequency from 1:1 to 1:2 for 3-4 hours.

3. Then ↓ balloon frequency to 1:3 for 3-4 hours, before finally terminating IABP support and removing the catheter.

Usual weaning process may take 10-12 hours.

c) Removal of a balloon catheter:

If the catheter is introduced into a femoral artery via a Gore-Tex sleeve, remove the catheter, ligate Gore-Tex sleeve, and trim the sleeve, leaving a short stump / or repair the femoral artery by a direct suture using 7/0 prolene.

d) Expected outcomes:

70% of patients may be successfully weaned from the IABP and the long term survival is about 60%. In selected children with refractory low cardiac output, after open heart surgery, > 50% long term survival is expected.

The mean duration of balloon pump support is 127 hours, with a range of 12-260 hours both in a long and short term survivors. Follow all long term survivors in the outpatient clinic with serial echocardiograms.

11.1.6 IABP Complications

1. Limb ischemia.

2. Cerebrovascular accidents and renal and mesenteric ischemia. It occurs due to excessive balloon length and inappropriate size in small children.

Mesenteric ischemia may present as a difficult diagnostic problem in infants.

3. Augmentation problems:

Supra-systolic augmentation may not be achieved even at maximum inflation of a balloon. This is frequently seen in patients < 2 years of age.

Supra-systolic augmentation could often be achieved by induced peripheral vasoconstriction (i.e., by active cooling of the patient to a core temperature of 34 ℃ and suppress tachycardia > 200 beats/min).

11.2 Extracorporeal Membrane Oxygenation (ECMO)

It is established treatment of severe but amenable lung or heart failure in neonates and children. The principle of extracorporeal circulation during CPB is applied and adapted for a long-term use.

Forms of ECMO: The most common are veno-arterial (VA) and veno-venous (VV).

A. Blood is drained from the venous system in both modalities.

B. Oxygenation of blood is through an oxygenator (membrane).

C. Blood is returned to venous system in VV ECMO, but no cardiac output is provided. VV ECMO can provide sufficient oxygenation for several weeks.

D. Blood is returned to arterial system in VA ECMO and cardiac output is provided.

E. Circuit is primed with blood.

ECMO is commonly used in neonatal intensive care units for newborns in pulmonary distress and in some pediatric patients.

11.2.1 Initiation of ECMO

A) In the operating suite:

Cannulae are placed into the large blood vessels (SVC, aorta), similar to open heart surgery for veno-arterial (VA) ECMO, and the cannulae are connected to ECMO circuit.

B) In the intensive care unit:

Small incision is made along the right side of the neck.

A cannula is placed in the internal jugular vein in the neck (IJV), leading to the right atrium of the heart. For veno-venous ECMO, another cannula is placed in the femoral vein for blood return. For a veno-arterial ECMO, another cannula is placed in a large artery (carotid artery or femoral artery) (see Figure 33). The cannulas are connected to the tubing of the ECMO machine and bypass circulation is begun.

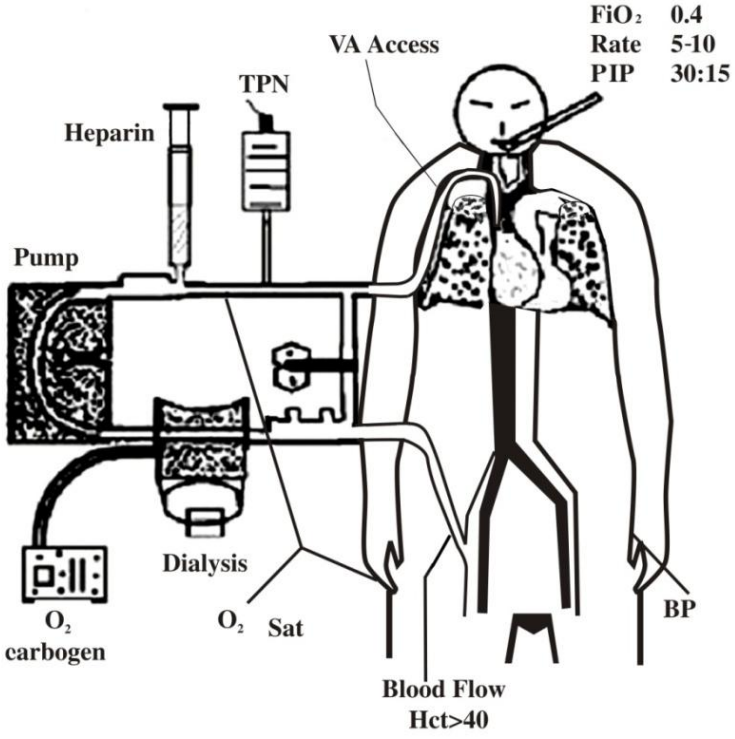

Figure 33 *Veno-arterial extracorporeal membrane oxygenation circuit in cardiorespiratory failure: Blood is drained from the right atrium through a canula placed in IJV and returned to (AO). Cardiac output is provided. Oxygenation can be provided for several weeks by veno-venous ECMO. IJV=internal Jugular vein, AO =aorta.*

11.2.2 Indications for ECMO

A. Neonates:

It is indicated in right, left, and biventricular failure with a low cardiac output subsequent to repair of a congenital heart defect. Primary pulmonary hypertension of the newborn (PPHN), meconium aspiration syndrome, respiratory distress syndrome, streptococcal sepsis (group B), asphyxia, and congenital diaphragmatic hernia (CDH) are other common indications.

Selection criteria for ECMO in neonates with respiratory distress:

i) Reversible lung injury, no major untreatable cardiac malformation or lethal malformations, no coagulopathy, and no major intracranial hemorrhage.

ii) On mechanical ventilation for 10-14 days or less and failure of maximal medical therapy, with gestational age > 34 weeks (relative criteria) or birth weight > 2 Kg (relative criteria).

Qualifying criteria for ECMO in infants with respiratory distress:

These are applied only when the infant has reached maximal ventilatory support of FiO_2 1.0, with a peak inspiratory pressures (PIP) as high as 35 cm H_2O.

1) Alveolar-arterial (A-a) gradient of 600-624 mm Hg for 4-12 hours at sea level.

$(AO_2 - aO_2)$ gradient = (PB mm Hg – water vapor pressure in mm Hg) $- \frac{(PaCO_2 + PaO_2)}{FiO_2}$

PB, 760 mm Hg, water vapor pressure, 47 mm Hg. The calculation should be made on FiO_2 of 1.0

2) Oxygenation index (OI) > 40 in 3 of 5 (postductal gas) samples obtained 30-60 minutes apart.

Equation:

$$OI = \frac{(MAP \times FiO_2 \times 100)}{PaO_2 \ for\ 2\ to 12\ hours.}$$

MAP = mean airway pressure in cm H_2O.

3) Acute deterioration with any one of the below:

a) PaO_2 less than or equal to 30-40 mm Hg for 2 hours.

b) pH less than or equal to 7.25 for 2 hours.

c) Intractable hypotension.

ECMO in pediatric patients:

Indications:

1. Right, left, and biventricular failure with a low cardiac output (CO) post - repair of a congenital heart defect (CHD). It is a frequent indication in neonates as well. 2. Pulmonary vasoreactive crisis with severe hypoxemia, and / or low CO post-repair of CHD. 3) Bridge to cardiac surgery in profound low CO with end-organ damage related to CHD. 4) Bridge to cardiac transplant. 5) Bridge to recovery from cardiomyopathy secondary to renal failure, myocarditis, and burns.

There are no clear set of inclusion or exclusion criteria exists for ECMO use in pediatric patient. Assessment of the patient's condition and the institutional experience dictates its use.

11.2.3 Patient Management on ECMO

A. Pulmonary system (These are often applied for neonates in respiratory failure):

i) Ventilator settings:

Intermittent ventilation (IMV) rate of 10 to 20/min.

FiO_2 of 0.30, PIP of 15-25 cm H_2O.

Positive end-expiratory pressure (PEEP) of 3-5 cm H_2O.

High PEEP of 12-14 cm H_2O may be used to avoid atelectasis.

ii) Pulmonary toilet:

It should be strict and require frequent ET suctioning, usually every 4 hours depending on secretions.

iii) Chest radiograph: It is taken daily.

End points: Await pulmonary recovery to be accomplished.

B. Cardiovascular system:

i) Systemic perfusion:

The perfusion should be adequate, and maintain adequate ECMO flows and intravascular volume. The flow rates range from 100 mL/kg to 125 mL/kg.

The volume status is assessed clinically by urine output and physical signs of perfusion.

ii) Maintain stable hemodynamics:

Assure adequate central venous pressure and mean arterial blood pressure.

Above may assure adequate intravascular volume.

iii) Inotropic agents:

May be used to enhance patient (native) cardiac output.

iv) Echocardiogram:

1. Excludes any major heart anomaly that requires immediate intervention if ECMO is initiated prior to a definitive diagnosis as in respiratory distress (due to obstructed total anomalous pulmonary venous connection).

2. To monitor progress or improvement in ventricular function.

C. Central nervous system:

CNS complications are related to the degree of hypoxia and acidosis.

Avoid paralytic agents and perform regular neurologic examinations.

Get head ultrasound before beginning ECMO in a neonate.

Reevaluation with serial head ultrasounds may be needed on a daily basis after any major event.

Give aggressive treatment for patients with seizures or suspected seizures (i.e., Rx with phenobarbital).

D. Renal system:

i) Oliguric phase: Oliguria during first 24-48 hours on ECMO may result in acute tubular necrosis (associated with capillary leak and ↓ intravascular volume as ECMO triggers an acute inflammatory like reaction).

ii) Diuretic phase: It begins within 48 hours on ECMO and it is earliest sign of renal recovery. But if oliguria persists > 48-72 hours, one may use diuretics and add hemofiltration / hemodialysis filter to the circuit if renal failure does not improve.

E. Hematologic considerations:

i) Hemoglobin: Maintain at 12-15 gm% using packed red blood cells (PRBCs).

ii) Platelets: Give platelet infusions to maintain platelet counts > 100,000 (as platelet consumption occurs during ECMO).

iii) ACT (activated clotting time): Maintain at 180-240 seconds to avoid bleeding complications.

F. Infection control:

Strict aseptic precautions are required.

Obtain cultures from the circuit at least once per day. Based on institutional experience, the protocol frequency may vary.

Appropriate cultures (e.g., fungal and viral) should be sent as needed.

G. Fluids, electrolytes, and nutrition:

Require close monitoring of fluids and electrolytes.

Patient's weight increases in the first 1-3 days on ECMO because of fluid retention. High-energy requirements are met using hyper alimentation techniques (see Chapter 8).

H. Commonly used medications:

i) Sedatives: After stabilization, minimal sedation either with fentanyl, midazolam, or morphine is required.

ii) Inotropic drugs: ↓ dopamine, dobutamine, and epinephrine doses, once ECMO is on.

iii) Diuretics: Furosemide is required for mobilization of tissue fluids (see Chapter 16-B).

iv) Gastric antisecretory drugs: Use H_2 antagonists for a prevention of GI tract bleeding (see Chapter 16-G).

v) Phenobarbital: It is often used for treatment of seizures (see Chapter 16-A).

vi) Antibiotics: These are given based on institutional experience (see Chapter 16-I).

11.2.4 ECMO Complications

(I) Mechanical Complications

1. Clots in the circuit:

It is the most common mechanical complication.

Major clot → oxygenator failure, consumption coagulopathy, and emboli.

2. Cannula placement technique:

Damage to the internal jugular vein and massive mediastinal bleeding.

Dissection of the carotid / femoral arterial intima may lead to aortic dissection.

3. Air in the circuit:

It ranges from a few bubbles to a complete venous air lock due to a dislodged venous cannula, a small tear in the vein wall, or high PO_2 in the blood may lead to this problem.

4. Oxygenator failure:

Results in ↓ exchange of oxygen or carbon dioxide or consumptive coagulopathy.

Replace membrane immediately.

5. Others: Cracks in connectors, pump, heat exchanger, and circuit and monitoring equipment malfunction.

Management of circuit failure:

Clamp the venous line immediately and open the bridge.

Clamp the arterial line, and remove the patient from the ECMO.

Bag the patient with FiO_2 of 1.0, or institute pre-ECMO ventilator settings immediately.

Fix the circuit problem.

(II) Hemorrhagic Complications

Bleeding is the most common complication of ECMO.

A head ultrasound is done every day to look for suspected intracranial bleed.

Hemorrhage at surgical site, cannula site, hemolysis, disseminated intravascular coagulation (DIC), intrathoracic, abdominal, or retroperitoneal hemorrhage may occur.

Thrombocytopenia (sequestration, dilution, ↓ production, ↑ consumption of platelets) may also be noticed.

(III) Cardiac Complications

1) Myocardial stunning: ↓ left ventricular shortening fraction by > 25% occurs at start of ECMO and returns to normal after 48 hours.

2) Hypertension: ↑ the risk of hemorrhage and stroke.

3) Arrhythmias: Occur due to hypoxia and electrolyte imbalance.

4) Symptomatic patent ductus arteriosus and pericardial tamponade.

(IV) Pulmonary Complications

Pneumothorax is a potential complication and as well pulmonary hemorrhage.

(V) Renal Complications

Oliguria: It is common during the early part of ECMO.

Acute tubular necrosis: Occurs in some patients and requires haemofiltration and/or dialysis.

(VI) Gastrointestinal Tract

Hemorrhage: Occurs due to stress, ischemia, or bleeding tendencies.

Direct hyperbilirubinemia and biliary calculi occur due to hemolysis and diuretic usuage, prolonged fasting, and TPN.

(VII) Neurologic & Vascular

Seizures, intracranial bleeding, brain infarction, and limb ischemia.

Cause: systolic hypertension, ligation of the carotid artery and IJV, cannulation of the femoral artery in larger children, heparinization, thrombocytopenia, and coagulopathies.

(VIII) Infection and Sepsis

The frequent manipulation in circuit increases the risk of sepsis.

(IX) Metabolic

Acid-base Distrubances: Acidosis or alkalosis.

Potassium: Hyperkalaemia or hypokalaemia.

Sodium: Hypernatraemia or hyponatraemia.

Calcium: Hypercalcaemia or hypocalcaemia.

Glucose: Hyperglycemia or hypoglycemia.

(X) Drug Serum Concentrations

Altered serum concentration of drug occurs due to increased volume of distribution.

Therefore, dose alterations of drugs may be necessary.

11.2.5 Weaning from ECMO

(I) Respiratory Failure

A trial period without ECMO is scheduled:

1. If the patient demonstrates adequate gas exchange, and is on reasonable ventilator settings.

2. If the patient tolerates a pump flow of 10-20 mL/kg/min with a minimum of 200 mL/min.

(II) Ventricular Dysfunction

If improved ventricular function is demonstrated on ECHO, and the patient tolerates gradual weaning of pump flows until 10-15 mL/kg.

11.2.6 Morbidity, Mortality, and Survival of ECMO

1) Oral feeding:

Despite normal suck and swallow reflexes, 33% have a feeding problem after ECMO.

2) Somatic growth:

Normal in infants who survive, poor growth should be evaluated due to other causes.

3) Bronchial asthma:

15% require oxygen a month after ECMO, and ↑ rate of hospitalizations occur for pulmonary conditions.

4) Nonpulmonary and surgical conditons:

Result in higher rate of re-hospitalization.

5) Neurological disabilities:

a) Sensorineural: Incidence of 6% (range, 2-18%); developmental delay of 9%.

b) Abnormal brainstem auditory-evoked response (BAER):

25% have mild-to-moderate threshold elevation.

c) Sensorineural hearing loss: Occurs after 1 year in 9% (range, 4-21%).

d) Cortical visual impairment: Mild degree is seen after posterior brain injury. The visual function improves usually in a long term.

Routine ophthalmic examinations during ECMO are not recommended.

e) Seizure disorders: By clinical and EEG criteria, 20-70% of neonates while are on ECMO, the incidence of epilepsy is 2% at the age 5 years.

f) Neuromotor deficits:

These are rare; mild hypotonia to gross motor delay and spastic quadriparesis may occur.

g) Psychosocial morbidity:

The social problems, academic difficulties at school, and attention deficit disorder may occur.

Mortality and Survival of ECMO:

In general, only 4% of all ECMOs are initiated for postcardiotomy patients.

44% of all ECMO instituted patients may be successfully weaned.

The immediate survival: (death occurrs in the first 24 hours after the de-cannulation). It is 66% in neonates, 33% in older infants.

The late survival: (death occurrs > 24 hours after the de-cannulation).

70% of late survivors have normal mental and somatic status.

11.3 Ventricular Assist Devices (VADs)

11.3.1 Indications

Patients awaiting heart transplantation, myocarditis, and cardiomyopathy that might achieve complete cardiac recovery.

Usage of VAD for several days to 14 months in children with myocarditis and cardiomyopathy increases survival and led to discharge of 78% of the infants under 1 year old.

11.3.2 Types of Devices (VADs)

True VADs are either extracorporeal pulsatile pneumatic system or implantable electrical systems of varying designs and functional principles.

1) VADs for use in children and adolescents:

(for BSA > 1.2 m^2 or children of age > 5 years)

i) Thoratec (Thoratec Laboratories Corporation), ii) Novacor (Baxter Healthcare

Corporation, Irvine, CA), and iii) The axial flow DeBakey VAD (Micromed Technology Inc., The Woodlands, TX).

2) VADs for use in small children and Infants:

(for BSA < 1.2 m^2 or age < 5-6 years)

Berlin Heart Excor and the Medos HIA device (miniaturized extracorporeal, pneumatic VADs).

(further discussion on VADs, the technique of insertion, postoperative management in patients on VADs is beyond the scope of this text).

B. Heart Transplantation

11.4 Care of a Heart Transplant Patient

11.4.1 Preoperative Care

It is paramount to optimize cardiac, renal, respiratory, neurologic, and metabolic functions of a child needing a heart transplant. This would ensure the best outcome after a transplant. Among all children waiting for heart transplantation, the mortality rate prior to transplantation is approximately 15-20%. For infants with hypoplastic left heart syndrome (HLHS), the mortality during the waiting period is significant when the infant has to wait > 3 months.

Other important measures:

A. Dctus dependent physiology: For patients with ductus dependent circulation, use lowest dose possible of prostaglandin. Usual dose: 0.1-0.2 mcg/kg/min.

B. Pulmonary and systemic blood flows: Balance the pulmonary and systemic blood flows by managing systemic arterial oxygenation. This may require adding nitrogen to the inspired gas mixture to render delivered oxygen at less than a fractional inspired oxygen (FiO_2) of 0.21 in certain infants.

C. Management of heart failure:

Optimize management of children with advanced heart failure.

D. Palliative surgical procedures:

Atrial septostomy:

For a significantly restricted interatrial communication, a balloon atrial septostomy or surgical septectomy may be necessary.

Stenting of the patent ductus arteriosus and pulmonary artery band (hybrid Norwood): It may be used to allow children of (HLHS) to wait for a transplant without prostaglandin E_1 (PGE_1) infusion. The child can be discharged and wait for a transplant outside the hospital.

11.4.2 Postoperative Care

Immediate postoperative management of a heart transplant child is similar to the management of any pediatric cardiac surgical patient with emphasis on maintenance of adequate perfusion, oxygenation by mechanical ventilation, fluid and electrolyte balance, maintenance of adequate renal

function, and prevention of infection. Specific details pertaining to postoperative care of heart transplantation are the following:

(I) Management of Pulmonary Hypertension

(The donor right ventricle is not tolerant of significant pulmonary hypertension and acute graft failure is one of the largest contributors to early mortality).

Mainstay therapy:

1. Sedation.

2. Hyperventilation (alkalinization).

3. Use of inotropic agents with minimal pulmonary vasoconstrictive effects.

4. Vasodilator therapy.

(Inhaled nitric oxide and sildenafil are used in this setting).

Sildenafil: A wide range of doses and patient variability has been reported, therefore, careful dose titration is necessary.

Pulmonary hypertension control: 0.5 to 3 mg/kg/dose orally every 6 to 12 hours.

Facilitation of inhaled nitric oxide wean after pulmonary hypertension control:

0.3 mg/kg/dose orally is given once 70 to 90 minutes prior to inhaled nitric oxide discontinuation.

Neonates and infants: Multiple dose therapy is given consisting of 0.22 to 0.47 mg/kg/dose every 6 hours to facilitate weaning from inhaled nitric oxide in patients who have previously failed (average duration: 28 days).

(II) Prostaglandin Therapy

For patients receiving PGE_1 prior to transplantation, continue for at least 1-2 days and then wean gradually over 3-5 days to prevent rebound pulmonary hypertension.

(III) Broncho-Pulmonary Toilet

Many children receive larger donor organs than their native hearts. This may lead to compression of lung parenchyma. Aggressive pulmonary toilet is indicated and close observation for respiratory compromise is required, especially after the initial extubation.

(IV) Post Transplantation Medications and Perioperative Immunosuppression

1. Inotropes and vasodilators:

Isoproterenol is most commonly used. It maintains adequate heart rate for age of the patient and cardiac output. Other inotropes may be used as indicated. The following concentrations of drugs will allow easy variation of drug amount per mL to permit constant infusion rates at prescribed dosage.

Isoproterenol 1 mL/hr = 1 mg/kg/hr, Dopamine 1 mL /hr = 5 mcg/kg/min

Dobutamine 1 mL /hr = 5 mcg/kg/min,

Milrinone / Amrinone 1 mL /hr = 5 mcg/kg/min.

Epinephrine 1 mL /hr = 0.05 mcg/kg/min.

Norepinephrine 1 mL /hr = 0.05 mcg/kg/min.

Nitroglycerin 1 mL /hr = 1 mcg/kg/min.

Nitroprusside 1 mL /hr = 0.5 mcg/kg/min.

Tolazoline 1 mL /hr = 1 mg/kg/hr.

2. Anti-hypertensives:

Enalapril: 0.1-0.5 mg/kg/day po in divided doses.

Captopril: Infants: 0.25-0.6 mg/kg/dose, titrated upward in 2-4 doses.

Maximum dose: 4 mg/kg/day.

Children: 0.5-2 mg/kg/day every 8-12 hrs to a maximum of 6 mg/kg/day. Maximum dose 450 mg/24 hours.

Propranolol: 2-4 mg/kg/day po in 2 to 4 divided doses.

Metoprolol:1-5 mg/kg/day po in 2 divided doses.

Verapamil (25 mg/mL): 2-7 mg/kg/day po in 3 divided doses.

Nifedipine: 0.6 mg-0.9 mg/kg/day po in 3 to 4 divided doses.

Hydralazine: 0.75-3 mg/kg/day po in 2 to 4 divided doses.

Prazosin: 0.05 mg/kg as test dose, then 0.25 mg to 1.5 mg/kg/day po in 4 divided doses.

Minoxidil: 0.2-1.0 mg/kg/day po in 1 or 2 doses.

3. Calcium channel blockers:

These are used as prophylaxis for post-transplant coronary artery disease and to improve renal perfusion.

Verapamil: Infants < 6 months of age: 5 mg/kg/day, 3 divided doses.

Diltiazem: Infants > 6 months of age:1 mg/kg/day, 2 divided doses.

4. Prostaglandin (PGE_1): Initial dose is started at 0.05 micrograms/kg/min; weaned off over several days (5 to 7 days) following transplantation. Most commonly used for patients on PGE_1 prior to transplantation or for patients in whom pulmonary hypertension is anticipated.

5. Antimicrobials for prophylaxis:

Cefazolin: Give until central lines are removed. Further antimicrobial therapy depends on specific culture results.

Infants < 1 month: 20 mg/kg/dose IV every 12 hours.

Infants > 1 month: 25 mg/kg/dose IV every 8 hours.

6. Antiviral drugs:

a. Ganciclovir: Used in recipients who receive CMV positive grafts as a specific treatment for CMV.

Dose: 10 mg/kg/day, in divided doses q. 12 hours for 14-21 days.

Decrease the dose for renal insufficiency.

b. Acyclovir:

Used as a prophylaxis against CMV. Not necessary to use if gancyclovir has been given.

Dose: 30 mg/kg/day divided t.i.d. for 3 months after transplantation.

7. Anti-platelet drugs:

Aspirin: 3-5 mg/kg/day, if platelet counts are chronically > 500,000.

Give 1/2 baby ASA tablet for infants.

8. H_2 Receptor antagonists:

Ranitidine (Zantac): Give while administering methylprednisolone.

Dose: Intravenous: 1-2 mg/kg/day divided q. 6 to 8 hours.

Oral: 2-4 mg/kg/day divided q. 12 hours (15 mg/mL solution).

9. Immunosupressive drugs:

A. Cyclosporine: IV infusion is maintained at 0.1-0.2 mg/kg/hour.

Start oral cyclosporine when oral feedings are well tolerated.

Dose of 10-20 mg/kg/day is given in divided doses every 8-12 hours.

Measure blood levels of cyclosporine daily until stable, then twice a week.

Maintain a target level of 250-300 nanograms per mL (whole blood).

A child < 4 years of age should receive t.i.d. dose due to rapid metabolism in younger children.

Infants with impaired renal function may be maintained on lower target ranges.

Infants with absorption problems may be given intravenous preparation of cyclosporine orally. Cyclosporine dosage may also need to be adjusted because of drug interactions.

B. Azathioprine:

3 mg/kg/IV or orally once daily. Start on first postoperative day.

May be given during pre-transplant period in older children and adolescents.

Dose is adjusted to keep WBC count > 4000 /mm^3.

C. Methylprednisolone (solumedrol):

20 to 25 mg/kg IV every 12 hours ×4 doses during the first two days after transplantation.

20-25 mg/kg IV every 12 hours ×8 doses for treatment of rejection.

D. Prednisone:*

0.15 mg to 0.3 mg/Kg/day. Wean over 3 to 6 months period.

Maintain at 0.1 mg/Kg/day after 6 months in patients without rejection.

(*Protocols using double drug therapy (cyclosporine and azathioprine, or methotrexate) for maintenance would not use this drug, to prevent graft atherosclerosis and chronic-steriod induced complications).

(* Protocols using triple drug therapy (cyclosporine, azathioprine, and steroid) for maintenance would discontinue this drug after long term in children).

E. Mycophenolate mofetil (Cellcept).

Commonly used for recalcitrant rejection and would replace methotrexate.

Used also as an alternative to azathioprine for maintenance therapy.

Experience is limited for use in young children.

Dose: 250 mg po b.i.d., gradually advance to a maximum dose of 2 gm per day (older children and adults).

Patients are at an increased risk of developing lymphomas and skin malignancies.

Common side effects: Increased susceptibility to infection, lymphoma, diarrhea, leukopenia, sepsis (generally CMV viremia), and vomiting.

F. Antithymocyte serum (ATS):

Used as a rescue therapy during episodes of moderate or severe acute rejection and/or is unresponsive to steroids.

It is also used also as a prophylaxis after transplant for infants > 30 days of age.

Dose: 0.5 mg/kg/dose IV for 7-10 days.

G. Antithymocyte globulin (ATGAM):

Used as a rescue therapy during episodes of moderate or severe acute rejection and/or is unresponsive to steroids.

Dose: 15 mg/kg/day for 7-10 days.

H. Methotrexate:

It is an alternative rejection treatment or for a maintenance therapy.

Dose: 10 mg/m^2/week.

Administered as a single dose or as 3 doses given q. 12 hours, or 3 times weekly.

Keep WBC count > 3000 /mm^3.

I. Tacrolimus (FK506/Prograf):

Used for recalcitrant rejection or maintenance immune-supression alternative to cyclosporine.

Induction drug level is 10-15 ng/mL for 3 weeks.

Maintenance drug level is 8-10 ng/mL.

FK506 should be administered at least one hour prior to, or 2 hours after feeding.

J. Intravenous immune globulin (IVIG, Sandoglobulin):

Dose: 400 mg/kg (12% solution) intravenously.

Repeat the dose × 2 during the 1st week after a transplantation.

Repeated doses may be given if increased immune suppression is needed.

Dose of 2 gm/kg (9% to 12% solution) may be used for severe rejection or prior to re-transplantation.

K. Sirolimus, Rapamycin (rapamune):

The drug is for use only in older children > 13 years and adults with solid organ transplants.

It should be used in combination with cyclosporine and corticosteroids for the first 12 months following transplantation.

After first 12 months following transplantation, any adjustments to the immunosuppressive regimen should be considered on the basis of the clinical status of the patient.

Dose: Initiate with a loading dose of up to 15 mg on day 1 post-transplantation.

Give an initial maintenance dose of 5 mg/day on day 2 post-transplantation and thereafter. A trough level should be obtained between days 5 and 7 to adjust the daily dose. Careful attention to clinical signs/symptoms, tissue biopsy findings, laboratory parameters, and drug concentration should form the basis for adjustment of the dose. Frequent dose adjustments based on non-steady-state drug concentrations can lead to overdosing or under dosing because sirolimus has a long half-life. Once sirolimus maintenance dose is adjusted, patients should continue on the new maintenance dose for at least 7 to 14 days before further dosage adjustment.

Calculate the new dose as below:

$$\text{New rapamune dose} = \text{current dose} \times \frac{\text{target concentration}}{\text{current concentration}}$$

A loading dose should be considered, in addition to the new maintenance dose when it is required to increase sirolimus trough concentrations.

$$\text{Sirolimus loading dose} = 3 \times (\text{new maintenance dose} - \text{current maintenance dose})$$

Maximum dose administered on any day should not exceed 40 mg.

Monitor trough concentrations for at least 3 to 4 days after a loading dose.

L. Total lymphoid irradiation (T.L.I.):

It is reserved for severe chronic rejection, unresponsive to other therapies.

One should not withdraw other immunosuppressive drugs until effect of TLI is documented. Total dose is 800 rads.

11.4.3 Protocol for Perioperative Immunosupression

Several protocols exist for preoperative immunosupression. The general guidelines for perioperative immunosupression and maintenance immunosupression are discussed below:

(I). Mainstay therapy:

It consists of drugs A+B+C+D+E as described below:

A 1) Cyclosporine:

Give 0.1 mg/kg/h IV when the donor is identified, it is stopped during surgery, and is restarted after transplantation. It is switched to po when possible,

Alternate dosing schedules for cyclosporine:

IV infuson: 2 to 4 mg/kg/day once a day over 4 to 6 hours / or

1 to 2 mg/kg / twice a day over 4 to 6 hours / or

2 to 4 mg/kg/day as a continuous infusion over 24 hours.

Oral capsules: 8 to 12 mg/kg/day orally in 2 divided doses.

Oral solution: 8 to 12 mg/kg orally once a day.

Doses are usually titrated downward with time to a maintenance dose as low as 3 to 5 mg/kg/day. All doses should be adjusted to achieve the desired therapeutic concentration.

(maintain a target trough cyclosporine level of 250-300 ng/mL).

Or

A 2) Tacrolimus (FK506):

0.15 mg/kg Orally or 0.03 mg/kg IV during pretransplant period.

If tacrolimus is used preoperatively, continue postoperatively, and begin the dosing when the patient is stable postoperatively with diuresis.

Dose: 0.075 to 0.15 mg/kg/day or 0.0015 mg/kg/hour IV infusion.

Adjust the dosing to trough whole blood (ELISA) level of 15 to 20 ng/mL.

In addition to either cyclosporine or tacrolimus give the following drugs.

B 1) Azathioprine:

2 mg/kg IV infusion is given over 1-2 hours during pretransplant period.*

(* Given in older children and adults)

2 to 3 mg/kg/day is administered postoperatively for all patients.

Adjust the dose to maintain a WBC count of at least 5 $\times$1000 / mm^3.

Or

B 2) Mycophenolate mofetil (MMF, Cellcept):

Give IV or orally at 500 mg/m^2/dose during pretransplant period.

Give IV or orally twice daily at 500 mg/m^2/dose during postoperative period.

Adjust the dose to maintain an MMF level of 2.5-5 mcg/mL and a WBC count of at least $4 \times 1000 / mm^3$.

C) Methylprednisolone:

Give 20 mg/kg/IV every 12 hours for 4 doses.

(May give one dose of methylprednisolone intra-op at the time of induction or after CPB is discontinued).

D) Antithymocyte globulin (Thymoglobulin) (induction immunosupression therapy):

It is given in children older than 30 days at a dose of 1.5 mg/kg/day once daily for the first 5 days.

E) Prednisone:

0.3 mg-0.15 mg/kg/day. Wean over 3 to 6 months period.

Maintain at 0.1 mg/kg/day after 6 months in patients without rejection.

(Some protocols omit in children)

(II). Adjunctive therapy:

A) Intravenous immune globulin:

Give a dose of 2 g/kg administered at 500 mg/kg/day for 4 days.

Daily dose is given over 12 hours, beginning right after the transplantation.

B) Ranitidine:

Give while the patient is receiving methylprednisolone.

C) Ganciclovir:

Give for 2 weeks in recipients who are CMV positive or who receive a CMV-positive donor.

Dose: 5 mg/kg IV over 1 hr every 12 hours for 14 days post-transplant.

D) Aspirin:

Give 3-5 mg/kg/day if the platelet count is chronically > $500 \times 1000 / mm^3$.

Immnuno suppressive medications at discharge:

Cyclosporine (Neoral): 10-20 mg/kg/day, is given orally, in divided doses every 8-12 hours depending on blood levels.

Azathioprine emulsion (Imuran) (10 mg/cc): 3 mg/kg/day, orally, once daily.

The following medications are taken during the first three months after transplantaion:

Poly-vi-sol, Acyclovir, Fer-in-sol, Nystatin.

(III). Maintenance of immunosupression:

1. Nnormal renal function;

All drug doses are adjusted based on history of rejection and drug toxicity.

Commonly used drugs:

A. Tacrolimus: 0.1 to 0.2 mg/kg/day or cyclosporine: 2.5 to 5 mg/kg/day.

B. Prednisone: 0.1 to 0.15 mg/kg/day.

(Some protocols omit prednisone in children).

C. Azathioprine: 1 to 2 mg/kg/day.

2. Abnormal renal function:

A) Methylprednisolone:

Give 20 mg/kg/IV every 12 hours for 4 doses.

(May give one dose of methylprednisolone 3-6 hours preoperatively. Start 1st postoperative dose 8 hours after arrival to ICU and 1 hour before OKT3).

B) Orthoclone (OKT3):

5 mg IV q. daily × 5 days, then 2.5 mg IV q. daily × 3 days.

Start 1st postoperative dose 10 hours after arrival to ICU.

C1) Azathioprine:

2 mg/kg IV infusion over 1-2 hours during pre-transplant period.

2 mg/kg/day postoperatively.

Adjust the dose to maintain a WBC count of at least 5×1000 / mm^3.

Or

C2) Mycophenolate mofetil (MMF, Cellcept):

Give IV or orally at 500 mg/m^2/dose during pretransplant period.

Give IV or orally twice daily at 500 mg/m^2/dose during postoperative period.

Adjust the dose to maintain an MMF level of 2.5-5 mcg/mol and a WBC count of at least 4×1000 / mm^3.

D) Prednisone:

0.25 mg / kg/q. 12 hours to start on 2^{nd} postoperative day, until 1^{st} biopsy is performed.

If biopsy is clean, taper to 0.15 mg/kg/q. 12 hours.

If biopsy is not clean, maintain 0.25 mg / kg/q. 12 hours until 2^{nd} biopsy, then initiate it taper.

E) Cyclosporine:

3-4 mg/kg/po q. 12 hours to be started on postoperative day 5 and is continued.

Dose is usually titrated downward with a time to a maintenance dose as low as 2.5 to 5 mg/kg/day. Dose should be adjusted to achieve the desired therapeutic concentration.

(Maintain a target trough cyclosporine level of 250-300 ng/mL).

11.4.4 Rejection Surveillance and Treatment

Routine endomyocardial biposies are mandatory since patients do not manifest EKG voltage changes or congestive heart failure, suggestive of rejection until late. High degree of suspicion is needed, and endomyocardial biposy is warranted to document rejection.

(I) Clinical Signs and Symptoms of Graft Rejection

a) General:

Irritability, malaise, changes in feeding pattern, changes in sleeping pattern, bradycardia, resting tachycardia, and changes in resting cardiac rhythm.

Presence of S_3 (third heart sound), S_4 (fourth heart sound), gallop rhythm, arrhythmias (supraventricular arrhythmias, premature ventricular contractions), conduction changes, and decreasing EKG voltage.

b) Signs and symptoms of decreased myocardial contractile function:

Cool and mottled extremities, oliguria, diaphoresis, and hepatosplenomegaly.

Echocardiographic evidence of reduced contractile function (♠ interpretation of rejection due to"remodeling" effects is taken into account if donor/recipient size mismatch is > 200%, and the child may require the administration of a calcium channel blocker to relax the myocardium).

c) Signs and symptoms of congestive heart failure:

Tachypnea, rales, hepatosplenomegaly, increasing cardiomegaly, and pulmonary edema and/or pleural effusion.

Rejection should be confirmed histologically in cases of persistent or equivocal signs and symptoms. Biopsy is also performed, in general, a week after completion of therapy for rejection. The endomyocardial biopsies are performed under echocardiographic or fluroscopic guidance, and the right heart catheteriezation may be performed at the time of biopsy. Usually 4 to 5 specimens are obtained for a procedure and may be placed in Hanks solution or preserved in formalin.

General time schedule for biopsies:

Every week ×6 weeks, then bi-weekly ×3. Then after first 3 months after transplantation, monthly for 6 months, and then nine months after transplantation. The intervals for biopsies may be determined on an individual basis.

Acute rejection should be treated using one of the rejection protocols.

(II) Clinical Symptoms and Signs Based Rejection Treatment

A. Asymptomatic and/or minimal symptoms:

Methylprednisolone:

Infants: 20-25 mg/kg q. 12 hours IV ×8 doses.

Older children: 250-500 mg every 12 hours ×8 doses.

Ranitidine: Used while on steroids.

Furosemide: Used as necessary.

Manage hypertension antihypertensive medications (see Chapter 16).

B. Moderate to severe symptoms:

Methylprednisolone: It is given as above.

Thymoglobulin (equine):

1.5 mg/kg/day IV for 7 days in ICU setting, or

Antithymocyte serum (rabbit):

0.5 cc./kg/day IV for 7-0 days in ICU setting, or

Antithymocyte serum (ATGAM) (equine):

15 mg/kg/day IV for 7-10 days in intensive care setting.

(dilute to 1 mg/mL in D5W or D5 $^{1}/_{2}$ NS).

Methotrexate:

10 mg/m^2 once a week; once a week.

Tacrolimus (FK506, Prograf):

One may consider conversion of treatment to use of tacrolimus.

OKT-3:

Rarely, it is used in young children.

Dose: 3-5 mg IV.

Administration: Give as a bolus for 5-10 days, infuse over 10 minutes.

Intravenous or oral steroid administration should continue while the patient is on OKT3.

Benadryl: 1 mg/kg/IV given slowly before OKT-3 infusion is begun.

Tylenol elixir or suppository (for age) is given as necessary.

Extracorporeal membrane oxygenation (ECMO):

Optional rescue therapy.

Ranitidine:

Oral dose: 2-4 mg/kg/day divided every 12 hours

IV dose: 1-2 mg/kg/day in divided doses every six to eight hours

Furosemide: as necessary

Emergency kit:

It is used in case of anaphylaxis

Methylprednisolone (125 mg), epinephrine (1:10,000), and benadryl (50 mg)\

***(III) Treatment Based on Histological Grading of Rejection by Endomyocardial Biopsy & Histological Grading of Rejection**

Histological grading of rejection:

A. No therapy needed (grade 0 to 2):

1. No rejection (Grade 0):

Sparse lymphoid infiltrates are present on biopsy specimens.

2. Mild rejection (Grade 1A):

Focal perivascular or interstitial infiltrates are present with mild intensity.

3. Focal moderate rejection (Grade 1 B):

Diffuse but sparse infiltrates are present as 1A, but there is no myocyte damage.

4. (Grade 2):

Only one focus with aggressive infiltration and/or a focal myocyte damage.

B. Grades with treatment threshold:

Low moderate rejection:

1. Grade 3A:

Multifocal aggressive infiltrates are present and/or presence of myocyte damage.

(Multiple foci may be present in only one fragment or scattered throughout the several fragments).

2. Grade 3B:

Diffuse inflammatory process.

The intensity of the lymphoid infiltrate may vary but > 1B.

The important feature of this grade is the presence of myocyte damage.

Myocyte damage must be present in at least 2 fragments, and some degree of infiltration is present in most fragments.

3. Severe acute rejection (Grade 4):

Diffuse and polymorphous infiltrate with or without edema, hemorrhage, and vasculitis. The infiltrate is more intense and more widespread than 3B with a conspicuous myocyte damage.

***(IV) Treatment of Rejection**

Several protocols exist for treatment of rejection. The general guidelines of rejection therapy based on histology, clinical and hemodynamic changes are discussed below:

1) Mild rejection (Grade 1A and Grade 1 B):

No treatment needed. Re-biopsy in one month.

2) Focal moderate rejection (Grade 2):

a) Azathioprine or cellcept: Maintain the dose, the patient is currently on.

b) Cyclosporine: Maintain the dose, the patient is on and recheck levels.

c) Prednisone: Dose is maintained or increased to 0.15 to 0.25 mg/kg q.12 hrs × 7-14 days.

(dosage depends on clinical condition and the time since the transplant, and taper prednisone dose to the maintenance dose level over 10 days).

3) Low moderate rejection (Grade 3A, 3B):

A. Patients without hemodynamic alterations or with a minimal hemodynamic compromise:

Patients may be treated out-patient, but rebiopsy should be done 5-10 days after rejection therapy.

a) Azathioprine or cellcept: Maintain the current dose.

b) Cyclosporine: Maintain the current dose and recheck levels.

c) i. Prednisone:

(It is given in patients without hemodynamic compromise and/or > 6 weeks post-transplant):

1.5 mg/kg/day for 3 days, then at 0.15 to 0.25 mg/kg q. 12 hrs, and taper to the maintenance dose level over 10 days.

Or

c) ii. Methyl prednisolone:

(It is given in patients with minimal hemodynamic compromise and/or < 6 weeks post-transplant):

5 to 20 mg/kg/IV daily × 3 days (dose is dependent on degree of compromise or histology), then reinstitute prednisone at 0.15 to 0.25 mg/kg q. 12 hrs, and taper to the maintenance dose level over 10 days.

B. Patients with moderate or significant hemodynamic compromise (Grade 3 A, 3 B & Grade 4):

Patient should be admitted. Re-biopsy should be done 5-10 days after rejection therapy.

a) Grade 3A with moderate hemodynamic compromise and > 6 weeks post-transplant:

Methyl prednisolone 5 to 20 mg/kg/IV daily ×3 days, and follow the same drug protocol as in A: (a+b+c ii).

b) Grade 3A and 3B with significant hemodynamic compromise and Grade 4:

a) Azathioprine or cellcept: Maintain the current dose

b) Cyclosporine: Maintain the current dose and recheck levels.

c) i). Orthoclone (OKT3):

5 mg IV q. daily ×4 days, then 2.5 mg IV q. daily ×3 days (if OKT3 antibody screen is negative).

Or

c) ii). Horse antithymocyte globulin (HATG)' Replace 'screen ispositive)' with 'screen is positive):

5 mg/kg daily ×5 to 7 days.

d) Methyl prednisolone 1.5 mg/kg/IV daily ×3 days, 1 hour before OKT3 or HATG administration, then give the drug below i.e., e).

e) Prednisone:

0.25 mg/kg q. 12 hours on days 4 to 7. Begin to taper to a baseline dose on day 8.

***(V) Treatment of persistent rejection**

A. Grade 3A, 3B and 4 with hemodynamic compromise:

a) HATG: 5 mg/kg/day IV ×5 to 7 days.

b) Methylprednisolone: 1.5 mg/kg IV on day 1, 1 hour before HATG administration.

c) Prednisone: Hold on day 1, but to continue the maintenance dose daily.

d) Azathioprine or cellcept: Maintain the current dose.

e) Cyclosporine: Maintain the current dose and recheck levels.

f) Rebiopsy in 5 days.

B. Grad 3A, 3B and 4 without hemodynamic compromise:

a) Azathioprine or cellcept: Maintain the current dose.

b) Cyclosporine: Maintain the current dose and recheck levels.

c) Prednisone: Maintain the current dose.

d) Methotrexate:

0.1 mg/kg po two consecutive days every week, for 4-8 weeks or 10 mg/m^2/week; once a week.

e) Rebiopsy in 7-14 days.

C. Optional Treatments of Persistent Rejection::

Consider the following treatments:

1. Use of OKT3 if it is not used previously. 2. Switch to FK506.

3. Use of sirolimus. 4. Replacing azathioprine with cellcept.

5. Total lymphoid radiation. 6. Photopheresis. 7. ECMO. 8. Re-transplantation.

(*III, *IV, *V. Adapted from the protocol for Immunosupression in a heart transplant. Department of Cardiothoracic Surgery. Newark Beth Israel Medical Center, UMDNJ, New Jersey. Publication of 2001)

C. Heart-Lung Transplantation

11.5 Postoperative Management of a Heart and Lung Transplant

Management of a heart and lung transplant child is similar to the management of any pediatric cardiac surgical patient, with meticulous attention directed to cardiac and pulmonary support. The postoperative course consists of approximately a two week hospitalization period.

11.5.1 Cardiopulmonary Care

A. Cardiac support:

1. Maintain adequate perfusion: Maintain adequate blood pressure, cardiac rhythm, and heart rate for age (rate is usually kept at 110-120 bpm).

2. Management of pulmonary hypertension.

Institute measures to decrease pulmonary hypertension (see Chapter 4 & Chapter 11, section B. Heart transplantation).

Isoproterenol is commonly used to maintain adequate heart rate and decrease pulmonary hypertension.

B. Respiratory support:

Intubation and mechanical ventilation:

Usually requires for 24 to 48 hours after surgery.

(Early extubation is a goal of postoperative management as prolonged mechanical ventilation is associated with increased morbidity and mortality).

Following immediate postoperative measures would achieve the shortest intubation time:

1. Maintenance of adequate perfusion.

2. Maintenance of adequate gas exchange.

3. Maintenance of adequate renal function.

Rapidly wean FiO_2 to the lowest, and maintain PaO_2 > 70-75 mm Hg to avoid O_2 toxicity, and use PEEP of 3 cm to 5 cm H_2O.

Double lung or single lung transplantation requires prolonged intubation with paralysis and sedation to prevent pulmonary hypertensive crises.

Lung transplant recipients of cystic fibrosis, often require prolonged weaning, before extubation due to hypercarbia.

Use diuretics, renal doses of dopamine for diuresis, and avoid nephrotoxic drugs.

Diuretics are very important with the use of cyclosporine for immunosupression.

It is critical to follow the steps below to achieve the above goal of shortest intubation:

1. Ventilator support: Require careful ventilator management.

2. Management of fluid balance: It should prevent volume overload, hypotension, and renal dysfunction.

3. Meticulous handling and care to prevent infection.

11.5.2 Blood Volume and Fluid Balance

Keep patients hypovolemic during the first few days after surgery.

Optimize Hct and O_2 transport (see Chapter 5).

Use maximally concentrated intravenous medications. Use diuretics routinely.

(majority of patients experience postoperative pulmonary edema due to increased pulmonary vascular permeability that results from ischemia and reperfusion injury and due to the interruption of the pulmonary lymphatics).

11.5.3 Prevention and Treatment of Infection

Pay meticulous attention to hand washing technique.

(there is no evidence that treatment using isolation is more effective than meticulous attention to hand washing).

(I) Prophylactic Broad Spectrum Antimicrobials

Give 1st or 2nd generation cephalosporins and an aminoglycoside / or

3rd generation cephalosporins IV during first 7-10 days after transplant and may be continued during rest of hospitalization.

(II) Antimicrobials for Patients with Cystic Fibrosis

Anti-pseudomonas antimicrobials: These are given IV for 7-10 days.

IV drugs are followed by aerosolized tobramycin or colistin for 8 weeks.

(III) Pneumocystitis Prevention

Trimethoprim-sulfa: It is given only for 3 days / each week.

(IV) Cytomegalovirus Infection or Exposure

Gancyclovir:

5 mg/kg/IV daily for 6 to 9 weeks for CMV positive donor or recipient mismatch or infection.

(V) Surveillance Cultures (Blood, Sputum, Urine)

Performed routinely to isolate bacteria, fungus, or viral organisms and treat infections. The central lines, IV access sites, and ET tube are the source of bacteremia or pneumonias during 1st week post-transplant.

(VI) Fungal Infections

Aspergillosis:

Localized (pulmonary) or systemic aspergillus infection or tracheal colonization is common in cystic fibrosis patients. Give itraconazole or amphotercin B

Candidiasis:

Colonization is more common than invasive infection.

Treat infection with amphotercin B, fluconazole, or itraconazole.

(VII) Viral Infections

CMV infection:

The infection is diagnosed by positive sputum or positive buffy coat culture of bronchial washings.

i) Treatment of mild to moderate infection:

Acyclovir (oral): 80 mg/kg/day in 3 to 4 divided doses.

Acyclovir (IV): 1500 mg/m^2/day in 3 divided doses.

ii) Treatment of severe infection:

Foscarnet (phosphonoformic acid):

90 to 120 mg/kg/day as a single infusion, once daily for 14 to 21 days.

CMV immune globulin IV:

100 mg/kg infusion every other day for 3 days, then once a week based on CMV antigenemia assay.

Administration of CMV immunoglobulin:

Begin infusion at 15 mg/kg/hour, if no reaction occurs, double the infusion rate every 30 minutes until 60 mg/kg/hour, and complete the prescribed dose at this rate.

Varicella:

Give IV acyclovir:

Children < 1 year: 30 mg/kg/day in 3 divided doses for 7 to 10 days.

Children > 1 year: 1500 mg/m^2/day or 30 mg/kg/day in 3 divided doses for 7-10 days.

Herpes simplex:

Acyclovir (oral): 1000 mg/day in 3 to 5 divided doses 7-14 days.

Maximum dose 80 mg/kg/day in 3 to 5 divided doses.

Acyclovir (IV):

Children < 1 year: 15 to 30 mg/kg/day in 3 divided doses for 7 to 14 days.

Children > 1 year: 750 to 1500 mg/m^2/day in 3 divided doses / or

15 to 30 mg/kg/day in 3 divided doses for 7-14 days.

RSV (respiratory syncytial virus):

Give ribavirin as inhalation aerosol.

Continuous aerosolization: 12 to 18 hours/day for 3 to 7 days.

Aerosol concentration 20 mg/mL (6 g reconstituted with 300 mL of sterile water or NS).

(use with Viratek small particle aerosol generator).

Intermittent aerosolization: (high dose aerosol): 2 g over 2 hours 3 times / day.

Aerosol concentration 60 mg/mL (6 g reconstituted in 100 mL of sterile water)

Influenza A:

Give amantadine *

Dose: Children 1 to 9 years: 5 mg/kg/day in 2 divided doses, maximum 150 mg/day.

Children 10-12 years: 5 mg/kg/day in 2 divided doses, maximum 200 mg/day.

Adults: 200 mg/day in 1 to 2 divided doses.

(* duration of treatment is for 24 to 48 hours after patient becomes asymptomatic).

Measles, influenza B, and parainfluenza:

Give ribavirin as inhalation aerosol.

Continuous aerosolization: 12 to 18 hours/day for 3 to 7 days.

Aerosol concentration 20 mg/mL (6 g reconstituted with 300 mL of sterile water or NS).

(Use with a Viratek small particle aerosol generator).

Intermittent aerosolization: (high dose aerosol): 2 g over 2 hours 3 times / a day.

Aerosol concentration 60 mg/mL (6 g reconstituted in 100 mL of sterile water).

Epstein-Barr (EB) virus:

Supportive and symptomatic treatment only.

11.5.4 Immunosuppression Medications

See below for detailed discussion.

11.5.5 Transfer Out of Intensive Care

It is done after inotropic and pressor medications are discontinued, and the patient is extubated and stable; thoracic catheters, arterial, and central venous access lines are removed. Continue the intravenous antibiotics while the patient is in the hospital.

11.5.6 Physical Therapy and Rehabilitation

It is initiated in the intensive care unit, and is increased in intensity as the patient becomes ambulatory. In order to minimize nosocomial infection, facilitate rehabilitation and discharge patients from hospital to post-transplantation housing that is near the thehospital. Here, patients continue to attend regular sessions of physical therapy.

11.5.7 Bronchoscopy and Transbronchial Biopsy

The timing of surveillance bronchoscopy procedures varies from centre to centre.

11.6 Immunosuppressant Therapy of a Heart-Lung Transplant

11.6.1 Induction Immunosuppression

Induction immunosuppression may be used in an attempt to minimise the risk of development of brochiolitis obliterans (BO). Acute rejection is a well established risk factor for the development of BO.

It has not been definitive that these agents are effective in achieving this outcome, therefore, usage is not common and varies according to a treatment centre.

Agents used for induction are potent and increase the risk for infection postoperatively.

Induction agents:

A. Lympholytic agents. B. Interleukin (IL)-2 receptor antagonists.

A. Lympholytic agents:

Lympholytic agents contain antibodies to human lymphocytes and derived from animal serum. These agents are administered for 3 to 5 days immediately after transplantation.

For steroid-resistant rejection, treat by administereing for 10 to 14 days.

Adverse effects:

↑ incidence of infection.

↑ risk of post-transplantation lymphoproliferative disease (PTLD) and leukopenia.

Cytokine release syndrome (i.e., chills, fever, vomiting, diarrhea, and headache).

Agents:

1. Rabbit antithymocyte globulin (RATG) [thymoglobulin].

2. Muromonab-CD3 (OKT3) [orthoclone].

3. Equine antithymocyte globulin (lymphocyte immune globulin) [ATGAM].

Rabbit antithymocyte globulin (RATG) [thymoglobulin]:

Give 1.5 mg/kg body weight administered daily for 3 to 5 days.

Thymoglobulin should be infused over a minimum of 6 hours for the first infusion and over, at least, 4 hours on subsequent days of therapy.

Muromonab-CD3 (OKT3) [orthoclone]:

Pediatric patient < 30 kg: 2.5 mg IV once a day for 5 to 7 days.

> 30 kg: 5 mg IV once a day for 5 to 7 days.

Lymphocyte immune globulin [ATGAM]:

15 mg/kg/day for 3 to 5 days.

B. IL-2 Receptor Antagonists:

These are monoclonal antibodies that specifically bind to the IL-2 receptor on activated T cells. Some trails showed that these agents ↓ frequency of acute rejection in adult lung transplants. No evidence that these agents ↓ frequency of brochiolitis obliterans (BO) or acute rejection in pediatric lung transplants.

Agents:

1. Basiliximab (simulect). 2. Daclizumab (zenapax).

These agents differ in their half-lives and the number of doses required for immunosuppression.

Basiliximab (simulect):

It may be used as part of an immunosuppressive regimen that includes cyclosporine and corticosteroids.

Pediatric patients < 35 kg:

10 mg a dose × 2.

Pediatric patients > 35 kg:

20 mg a dose × 2.

The first dose should be given within 2 hours prior to transplantation surgery.

The recommended second dose should be given 4 days after transplantation. The second dose should be withheld if complications such as severe hypersensitivity reactions to simulect or graft loss occur.

Daclizumab (zenapax):

It is used with immunosuppressive regimen that includes cyclosporine and corticosteroids.

10 months to 17 years old: Administered as in adults.

1 mg/kg IV (15 minutes infusion) < 24 hour prior to transplant surgery, then 1 mg/kg IV q. 14 days × 4 doses.

11.6.2 Maintenance Immunosuppression

Corticosteroids are the most commonly used agents in pediatric lung transplant recipients followed by calcineurin inhibitors and cell toxins.

Three drug protocols utilize cyclosporine, azathioprine, and steroid.

Two drug protocols utilize FK506 and azathioprine /or cyclosporine and azathioprine.

A. Calcineurin inhibitors:

1. Cyclosporine and 2. Tacrolimus.

(See heart transplant section for a detailed dosing).

Cyclosporine:

0.25 to 0.5 mg/kg IV after transplant (given over 3-4 hours) then give 1.5 to 2.5 mg/hour, and adjust the infusion rate to maintain whole blood cyclosporine level of 300-350 ng/mL in the immediate postoperative period.

Tacrolimus:

It is given in the postoperative period when a patient is stable with diuresis.

0.075 to 0.15 mg/kg/day or 0.0015 mg/kg/hour IV infusion.

Both the above agents are the mainstay of immunosuppression.

Both are equal in prevention of BO and improvement of survival.

Drug levels should be monitored on a regular basis.

Doses for lung transplant recipients are usually maintained at higher levels than those for other organ transplants.

♣ Most pediatric lung transplant centres use tacrolimus-based regimen as their primary immunosuppression because it has a more manageable adverse effect profile in children.

Gingival hyperplasia and hirsutism that occur with cyclosporine negatively influence the compliance, particularly, in teenage patients. Aerosolised cyclosporine may provide a substantial survival advantage to lung transplant recipients receiving the drug.

Adverse effects:

Increased risk of infection, nephrotoxicity, neurotoxicity, GI disturbances, electrolyte derangements, malignancy, and hypertension.

Cyclosporine may cause gingival hyperplasia and hirsutism.

Tacrolimus may cause more hyperglycemia.

B. Cell toxins:

1. Azathioprine and 2. Mycophenolate mofetil (MMF, cellcept):

(see heart transplant section for a detailed dosing).

In lung transplantation, studies have not shown a clear benefit of one agent over the other.

Azathioprine:

Give 2 mg/kg IV during the pre-transplant period, 2 mg/kg IV during the postoperative period then 2 mg/kg IV daily until dosing of 3 mg/kg/PO is begun. Dosing is often determined by white blood cell count.

Adverse effects for both azathioprine and cellcept include myelosuppression, infection, and nausea. Azathioprine may cause hepatotoxicity and rash.

MMF may cause diarrhea and an increased risk of lymphoproliferative disorders.

MMF serum levels can be measured, and dosage is adjusted to maintain adequate serum levels.

C. Corticosteroids:

(see heart transplant section for a detailed dosing).

1. Methylprednisolone:

1 mg/kg / IV in the immediate postoperative period, then daily until PO steroid is begun. Steroids are the most commonly used group of immunosuppressant agents.

Adverse effects:

Hyperglycaemia, hypertension, growth suppression, bone loss, gastrointestinal disorders, acne, amenorrhea, cataract, and increased risk of infection. At high doses, it causes alterations in serum levels of the calcineurin inhibitors.

D. Rapamycin and derivatives (sirolimus and everolimus):

These agents can be used with either cyclosporine or tacrolimus.

(see heart transplant section for a detailed dosing).

Rapamycin (sirolimus) is rarely used during the first year post-transplant.

It has no role in the early postoperative period because of interference with wound healing. It causes anastomotic dehiscence and development of interstitial pneumonitis.

Fifteen percent of patients receive this agent by five years post-transplant.

These agents can be used as rescue therapy (for rejection) in renal dysfunction,

These agents are beneficial in patients with chronic rejection. These agents inhibit vascular injury in vivo and inhibits proliferation of endothelial and smooth muscle cells in vitro.

Dosing is once daily, but in children desirable drug levels are maintained with b.i.d. dosing.

Adverse effects: Hyperlipidemia and myelosuppression.

11.7 Clinical Surveillance of a Heart-Lung Transplant

11.7.1 Transbronchial Biopsy

First surveillance bronchoscopy is commonly performed within the 1st week after transplantation (it may be within the first 24 hours, in some centers while the patient is still intubated). This would assess bronchial anastomosis for blood supply, healing, and removal of secretions.

Transbronchial biopsy is performed under fluoroscopic guidance in two different areas of transplanted lungs for rejection surveillance.

Three to six biopsy specimens are obtained at each procedure.

Protocols for further surveillance transbronchial biopsy vary between treatments centers.

SVHS recommendation:

1. Transbronchial biopsy schedule of 3, 6, 9 to 12 weeks post-transplantation.

2. Additional transbronchial biopsy procedures for new-onset symptoms.

3. Follow-up transbronchial biopsy procedures for acute rejection or CMV pneumonia.

After 1st year post-transplant, transbronchial biopsy is performed every 6 months for surveillance of BO or in chronic mild rejection.

11.7.2 Bronchoalveolar Lavage

It is often performed in association with transbronchial biopsy for diagnosis and management of infections, viral cultures, and buffy coat cultures for CMV infection.

11.7.3 Open Lung Biopsy

It may not be necessary if adequate transbronchial biopsy specimens are obtained. If transbronchial biopsy specimens are inadequate, open lung biopsy is performed, especially after suspected rejection and inadequate clinical response to pulse steroid administration. Tissue specimen obtained by transbronchial biopsy may be inadequate for diagnosis of BO.

11.7.4 Pulmonary Function Tests

Monitor lung function, in addition to blood pressure, temperature, and daily weights. As rejection or infection frequently results in loss of lung function, children old enough to perform spirometry, FEV_1 estimation should performed 2 weeks after transplant and weekly thereafter. Spirometry and oximetry are performed at home and changes in daily values are monitored to detect rejection or onset of BO. In young children, who can not perform spirometry, pulse oximetry is monitored to detect early changes in lung function.

11.7.5 Echocardiography

It should be part of surveillance to evaluate cardiac function, and to detect any differential rejection of heart and lungs. Cardiac rejection is rare in the absence of pulmonary rejection, and cardiac rejection is less frequent in heart lung transplants than in cardiac transplants alone.

11.7.6 Therapeutic Drug Monitoring

It should be a part of the routine post-transplant protocol to prevent side effects from immunosuppressive agents.

11.8 Management of Rejection of Heart-Lung Transplant

Rejection of a heart lung transplant may be acute that occurs first few days after a transplant or chronic that may occur subtly in the course of a few weeks or months after transplantation.

(I). Acute rejection: Histology shows perivascular lymphocytic infiltration of lung which might extend into interstitial airways. The histological changes are graded from 1 to 4.

(II). Chronic rejection (BO, bronchiolitis obliterans):

Bronchiolitis obliterans is an inflamatory process of small airways with fibrotic and proliferative changes. It is presumed to be an immune mediated injury.

Late and sudden or progressive decrease in FEV_1 suggest onset of BO, even transbronchial specimens are not diagnostic.

11.8.1 Symptoms and Signs of Rejection

Dry cough, pyrexia, malaise, shortness of breath, and chest tightness with decrease in oxygen saturation are common.

Inspiratory crackles at bases and friction rubs on auscultation, decrease in oxygen saturation, chest rontegenogram showing new onset of pleural effusions or hilar pulmonary infiltrates that are often symmetrical, and pulmonary edema are all suggestive of rejection in the absence of pulmonary infection.

Chest x-ray may also be normal. Spirometry reveals decreased FEV_1 or FEF.

11.8.2 Treatment of Rejection

Acute rejection: Give pulse steroids.

Methylprednisolone:

Infants: 20-25 mg/kg q. 12 hours IV ×8 doses.

Older children: 250-500 mg every 12 hours ×8 doses.

(See heart transplant section for a detailed dosing).

Perform open lung biopsy if there is no rapid clinical response.

Chronic rejection: Give pulse steroids:

Methylprednisolone:

Infants: 20-25 mg/kg q. 12 hours IV ×8 doses.

Older children: 250-500 mg every 12 hours ×8 doses.

If there is no rapid response, give either:

1. Antithymocyte globulin or 2. OKT3.

(See heart transplant section for detailed dosing)

11.8.3 Treatment of Refractory Rejection

1. Antithymocyte serum (ATGAM) (equine):

15 mg/kg/day IV for 7-10 days is given in intensive care setting.

Dilute to 1 mg/mL in D5W or D5 $^{1}/_{2}$ NS / or give

2. Thymoglobulin (equine): 1.5 mg/kg/day IV for 7 days is given in ICU setting.

11.8.4 Treatment of Lymphocytic Bronchitis: (B1 or B2)

Methotrexate 0.1 to 0.2 mg/kg once a week / or

Immune globulin 100 mg/kg IV.