Heart transplantation

The first human heart transplant was performed by Christian Barnard on December 3rd, 1967, and 3 days later Kantrowitz completed the first pediatric heart transplant on a 16-day-old infant with Ebstein’s anomaly and pulmonary atresia. Unfortunately, during the first decade of heart transplantation, outcome was poor and very few pediatric heart transplants were performed until the 1980s, when cyclosporine became available and transplantation was proposed for neonates with complex congenital heart lesions such as hypoplastic left heart syndrome (HLHS) (Fig. 24.1). Since the mid-1990s, the number of reported pediatric recipients has remained stable despite improved survival, underlining the rate-limiting step of donor organ availability.

Organ transplantation in the USA is sanctioned by congressional mandate through the Nation Organ Transplant Act (NOTA). An Organ Procurement and Transplant Network (OPTN) was created and is administered by the United Network for Organ Sharing (UNOS). Donation of organs is voluntary and is managed by government-regulated local agencies called organ procurement organizations. Equitable allocation of a scarce life-saving resource is challenging. The UNOS has three recipient status categories—status IA, IB, and II, with status IA indicating the sickest patients who are in urgent need of heart transplantation for survival.

Indications for heart transplantation

Heart transplantation is generally indicated when expected survival is less than 1 or 2 years and/or when there is unacceptable quality of life secondary to irreparable cardiac diseases. Survival rates have increased as management and immunosuppressive techniques have improved and absolute contraindications for transplantation have now become more relative. Often the dilemma is no longer whether to transplant or not, but rather when to do it. However, heart transplantation can be a viable option for young patients with complex congenital heart disease or heart failure.

transplantation remains a palliative procedure at present. Pediatric indications for heart transplantation vary with age and include cardiomyopathy, congenital heart disease (CHD) and retransplantation (Fig. 24.2). The majority of transplantations in infants are for CHD, whereas cardiomyopathy is the predominant indication in older children.

Cardiomyopathy

Dilated cardiomyopathy
The etiology is diverse and incompletely understood but includes viral myocarditis, drugs (e.g. adriamycin), abnormalities of fatty acid, amino acid, glycogen and mucopolysaccharide metabolism, mitochondria and genetic disorders, chronic arrhythmia, and coronary artery abnormality. Predictors of a poor outcome are a family history of cardiomyopathy, syncope, ventricular arrhythmia or near-death episode, left ventricular end-diastolic pressure greater than 25 mmHg, and left ventricular ejection fraction less than 30%.

Hypertrophic cardiomyopathy
A number of genotypes are known. Risk factors for sudden death include marked left ventricular wall thickness, family history of sudden death, and non-sustained ventricular tachycardia.

Restrictive cardiomyopathy
These uncommon disorders with diastolic dysfunction generally have a poor prognosis and are associated with myocardial infiltrative processes such as amyloidosis, hemochromatosis, glycogen storage disease, mucopolysaccharidosis, sarcoidosis, and endomyocardial fibrosis. Elevated pulmonary vascular resistance ($PVR$) is often present.

Congenital heart disease
This group of patients include children with “failed” Fontan or equivalent palliation of single ventricle physiology, patients with end-stage failure after surgical repair of congenital defects, HLHS, and complex congenital heart variants with no option of palliative surgery.

One-year survival rates after surgery in excess of 80% have been achieved for infants with HLHS, irrespective of whether primary transplantation or staged reconstruction (Norwood approach) was performed. Most centers opt to perform staged reconstruction, partly because of the desperate paucity of donor organs and the significant mortality (up to 30%) while waiting for transplantation.

Other indications
Although rare, there are children who may require cardiac transplantation for unresectable cardiac tumors and other diseases such as Kawasaki’s syndrome.
Recipient evaluation

A detailed assessment of patients is required to determine their suitability for heart transplantation (Table 24.1). Factors that may exclude patients from consideration for transplantation include severe central nervous system, liver or kidney dysfunction, pulmonary infarction, pulmonary hypertension, morbid obesity, and some infections, malignancies or chromosomal abnormalities.

Assessment of cardiopulmonary function usually includes cardiac catheterization and angiography. The recipient’s cardiac anatomy has to be accurately delineated as abnormal cardiovascular anatomy influences surgical technique during harvesting and transplantation. Hemodynamic measurements are required, especially determination of PVR. Transplantation in patients with PVR in excess of 5 Wood U/m² or a transpulmonary gradient greater than 15 mmHg is potentially contraindicated because it is associated with acute right heart failure and increased mortality. The upper limit of PVR associated with successful cardiac transplantation has not been established in children.

All patients with pulmonary hypertension have PVR measured at baseline conditions and during administration of oxygen, nitric oxide and/or other pulmonary vasodilator therapy. When the response is marginal, repeat values after 1–2 weeks of inotropic support, afterload reduction, and pulmonary vasodilation may demonstrate improvement (see Chapter 14 for management of pulmonary hypertension). Experienced institutions may accept children with PVR as high as 8–12 Wood U/m² if it is reactive. Patients whose PVR does not respond to therapy may be candidates for heterotopic heart transplantation, heart–lung transplantation, or lung transplantation. Children with restrictive cardiomyopathy are particularly prone to marked elevation of PVR, which may contribute to the poor prognosis in these patients and potentially make cardiac transplantation problematic. Nitric oxide appears to be a good agent to demonstrate reversibility of PVR in these patients.

Radionuclide angiography is useful for assessing systemic ventricular dysfunction in patients with complex cardiac morphology. Endomyocardial biopsy can identify acute myocarditis and myocardial infiltrates. Pulmonary function tests (PFTs) may be indicated for older children with chronic lung disease. Evaluation of patients with cardiomyopathy should include a metabolic work-up because potential etiologic factors include mitochondrial disorders, and genetic studies if indicated by phenotypic appearance or family pedigree.

Infectious disease and immune system evaluation are important. The child’s immunization status should be updated if necessary. Tests are performed for latent infections such as cytomegalovirus or Epstein–Barr virus that may become clinically significant during immunosuppression. Donor matching is based on ABO typing. The candidate’s

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<td>Cardiomyopathy work-up</td>
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<td>Thyroid function tests</td>
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<td>Skeletal muscle biopsy</td>
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<td>Dental services</td>
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<td>Other services</td>
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INR, international normalized ratio; PPD, purified protein derivative.
PART 5  Anesthesia for specific lesions

blood is also screened for antibodies against sera of random blood donors and, if reactive, a serum crossmatch with the donor is performed. Although human lymphocyte antigen (HLA) compatibility may improve graft survival, HLA matching is not routinely performed because of time constraints and the limited availability of donor organs. Panel reactive antibodies (PRA) are preformed circulating HLA alloantibodies that, in high titer, are associated with reduced allograft survival. Therapies to reduce PRA levels have included intravenous immunoglobulin, plasmapheresis, and cyclophosphamide. Homologous blood products can increase antibody titers and should be avoided if possible during the pre-transplant period.

Heart transplantation requires long-term immunosuppression, frequent invasive procedures, and lifelong medical care. Patients have to live close to the hospital during the initial months after surgery and temporary relocation of the family may be necessary. Prolonged periods of stressful hospitalization are likely. A stable social situation is essential for success and psychosocial evaluation is an important aspect of the pre-transplantation process.

Recipient pre-transplant management

Mean waiting period from acceptance for heart transplantation to actual surgery currently is about 3 months but varies with the child’s age, blood group, and list status. Approximately 20% of children with cardiomyopathy and 30% of those with end-stage CHD die waiting for a donor heart. Aggressive medical management to achieve stabilization is required and includes supplemental oxygen, diuretics, inotropic support (e.g. dobutamine, dopamine, phosphodiesterase inhibitors), arrhythmia therapy, and mechanical ventilation. Children with chronic heart failure often receive digoxin, diuretics including spironolactone, and angiotensin-converting enzyme inhibitors. Studies of β-blockade therapy (e.g. metoprolol, carvedilol) have been limited in children but are encouraging. Patients with severe left ventricular dilation may need anticoagulation, preferably coumadin, to prevent the development of intracardiac thrombi and systemic embolization. Amiodarone is often chosen for treating arrhythmia. Implantable defibrillators have been effective in pediatric patients large enough for these devices. Biventricular pacing is an experimental modality showing promise.

Patients with refractory myocardial failure require mechanical circulatory support as a bridge to cardiac transplantation. Extracorporeal life support is the only modality currently available for small children and can be used for at least 2 weeks with acceptable survival and hospital discharge rates. Renal insufficiency requiring dialysis decreases the likelihood of survival. Other complications include sepsis, bleeding, and neurologic injury. Ventricular assist devices and intra-aortic balloon pumping are usually reserved for older adolescents but have been employed successfully in younger children weighing about 15 kg. Partial left ventriculectomy has been used to improve clinical status and acts as a biological bridge to heart transplantation in children with end-stage dilated cardiomyopathy. Congenital heart disease is the main indication for heart transplantation in children less than 1 year of age. Many of these infants have HLHS and are managed invasively in an intensive care setting. Patency of the ductus arteriosus is maintained initially by prostaglandin E1 (PGE1) infusion and may require stenting later. Restriction of flow across the atrial septal defect is addressed by interventional catheterization techniques. Balance between systemic and pulmonary blood flow is necessary, and occasionally may require pulmonary artery banding.

Donor management

Once the diagnosis of brain death is established and parental/guardian consent obtained, the donor’s specifics are checked for possible match with patients listed by UNOS for transplant. Because of the shortage of suitable organ donors and the high morality rate on the waiting list, most centers use a liberal donor screening strategy. The age distribution of pediatric heart donors is similar to that of heart recipients. Echocardiography is useful for assessment of donor heart function. Widespread malignancy or infection in the prospective donor are exclusion criteria, but cardiac resuscitation and chest trauma are not necessarily contraindications provided the donor’s hemodynamics have been stabilized and inotropic agents are no longer needed or are at minimal doses. Usually the donor should be 80–160% of the recipient’s weight, but the upper limit may be extended for neonates or for recipients with pulmonary hypertension. Attempts to limit donor heart ischemia time are important but may be hampered by transport issues. Many centers prefer the period to be less than 6 hours, especially if the recipient has increased PVR although successful outcomes after graft ischemia times of up to 9 hours have been reported. The anesthetic management of a pediatric organ donor is beyond the scope of this chapter and has been reviewed elsewhere.

Surgical technique

There are two methods for performing heart transplantation—orthotopic, in which the recipient heart is excised and replaced in the correct anatomical position by the donor heart, and heterotopic, in which the donor heart is placed in the right side of the chest alongside the recipient organ and anastomosed so as to allow blood flow through either or both hearts. The majority of transplants in children have been of the orthotopic type.
The orthotopic approach first described by Lower and Shumway\(^\text{21}\) has been employed for many years in cases where anatomy is straightforward. This technique avoids individual systemic and pulmonary venous anastomoses but results in capacious atrial chambers, comprising donor and recipient components, which contract asynchronously. It has been suggested that atrial contribution to cardiac output (CO) may be superior with near to total cardiac transplantation.\(^\text{22}\) A small cuff of left atrial tissue is left in place, incorporating all pulmonary veins, and the entire right atrium is removed. Bicaval anastomoses are then performed. This technique results in more normal anatomical result. It has been suggested that it improves sinus nodal function, invokes less tricuspid regurgitation, and improves exercise performance.\(^\text{23}\) However, there are only preliminary data in children to demonstrate that outcomes are improved.\(^\text{24}\)

Cardiac transplantation for children with congenital malformations can require surgery of greater complexity. Deep hypothermic circulatory arrest may be employed in patients requiring extensive vascular reconstruction; for example, Bailey's technique for transplantation in infants with HLHS.\(^\text{25}\)

**Anesthetic management**

**Pre-cardiopulmonary bypass period**

Children listed for heart transplantation have little or no cardiac reserve and can be extremely sensitive to the perturbations induced by anesthesia and surgery. For children with CHD, the pre-cardiopulmonary bypass (pre-CPB) anesthetic management for heart transplantation differs little from that for non-transplant cardiac surgery and requires a good appreciation of the patient's particular pathophysiology. The physiological consequences of cardiac failure are discussed in Chapter 3. In brief, children with end-stage cardiac dysfunction have a chronically activated sympathetic nervous system and an impaired response to \(\beta\)-agonists. Reduced renal perfusion triggers the renin–angiotensin system, which leads to increases in vasoconstriction, venoconstriction, and intravascular volume. These compensatory mechanisms increase preload and afterload and perpetuate congestive heart failure. Plasma norepinephrine levels are about three times normal, while myocardial norepinephrine concentrations are reduced. Cardiac \(\beta_1\)-receptors are downregulated and there is a partial uncoupling of cardiac \(\beta_1\)-receptors for adenylyl cyclase. Additionally, altered ratios of inhibitory/stimulatory signal transduction proteins decrease \(\beta_1\)-receptor sensitivity. These factors contribute to reduced levels of cyclic adenosine monophosphate with reduced movement of calcium into myocytes. The contractile response to direct \(\beta\)-adrenergic inotropes is impaired. Since tissue norepinephrine levels are decreased, indirect-acting agents such as ephedrine are also less effective.

A dysfunctional, dilated heart is exquisitely sensitive to changes in preload, afterload, heart rate (HR), and contractility. Systolic and diastolic function is impaired and high mean atrial pressure is required to ensure adequate filling. Elevated left atrial pressure results in elevated PVR and right ventricular dysfunction. Because these patients have exhausted their preload reserve, reduction in HR results in a decline in CO. Conversely, an increase in HR decreases the diastolic filling time which reduces end-diastolic volume and stroke volume. Small increases in afterload result in comparatively large increases in end-systolic volume leading to a large decrease in stroke volume and CO.

Prior to surgery, young infants and children with uncompensated heart failure are usually already in intensive care, and may have invasive lines in situ and be on ventilator support. More stable patients may have been called in from home for the transplantation surgery and could have eaten recently. Several hours usually elapse before surgery but therapy to modify gastric pH and volume and the application of continuous cricoid pressure during induction is reasonable. Good communication between the transplant surgeons, anesthesiologists, operating room staff, and donor procurement team is vital in order to coordinate care and ensure graft ischemia time is minimized. The advisability of premedication and the method of anesthesia induction depend upon the patient's age, cardiac lesion, and cardiopulmonary function. Establishing invasive hemodynamic monitoring prior to induction of anesthesia may not always be feasible and so it is imperative to institute non-invasive patient monitoring prior to the administration of medications that alter hemodynamic and/or respiratory function. Meticulous airway management is vital as hypoxia and hypercarbia aggravate PVR and may further depress CO. Similarly, anesthesia or surgery-induced changes in HR, preload, afterload or contractility may precipitate hemodynamic decompensation. Rapid sequence induction may be poorly tolerated in patients with a minimal cardiorespiratory reserve. A wide variety of anesthetic agents have been used successfully. The desirable and detrimental cardiovascular effects of anesthetic agents are reviewed in Chapter 4.

Monitoring during surgery does not differ from that used for pediatric open heart surgery. Some authorities avoid inserting catheters into the right internal jugular vein because...
the vessel will later be accessed repeatedly for endomyocardial biopsies. Transesophageal echocardiography (TEE) is useful for evaluation of heart anatomy and function, mural thrombus, and intracardiac air. Many experienced institutions do not use pulmonary artery catheters because the value of information gained does not warrant the additional risk. The prophylactic use of antifibrinolics should be considered. Aprotinin has been reported to diminish blood loss in children during heart transplantation if they have previously undergone median sternotomy. The value of antifibrinolics for primary heart transplantation is uncertain.

Cardiopulmonary bypass period
Ulrafiltration during CPB may benefit the patient by removing excess free water, hemoconcentrating red cells and coagulation factors, and modulating the inflammatory response. Diuretic therapy may be required. Methylprednisolone is administered to attenuate any hyperacute immune response; the timing and dose is institution-specific.

Post-cardiopulmonary bypass period
Issues of concern include denervated donor heart, global ischemia–reperfusion injury, elevated PVR, arrhythmia, hemostasis, and hyperacute rejection.

The transplanted heart is functionally denervated. The recipient atrial remnant remains innervated but no electrical impulses cross the suture line so the donor atrium is responsible for the patient’s HR. There are two P waves on the electrocardiogram (ECG), representing activity of the transplanted and native sinoatrial nodes. Resting HR is higher than normal because vagal tone is absent and the normal beat-to-beat variations in response to respiration are lost, as are the normal responses of the heart to alterations in body position and carotid body massage. The donor heart cannot abruptly increase HR and CO in response to stress because the baroreceptor reflex is disrupted. The attenuated HR response to stress means the anesthesiologist must be particularly vigilant to ensure the child does not become too lightly anesthetized. With the loss of the baroreceptor reflex, the patient with a denervated heart may initially show an exaggerated response to hypovolemia with a marked decrease in mean blood pressure, and then a delayed exaggerated hypertensive and tachycardia response, due to endogenous catecholamine release. The Frank-Starling (pressure-volume) relationship remains intact and compensates for hypovolemia and hypotension by increasing stroke volume secondary to an increased venous return. Therefore, it is important to maintain adequate preload, especially if vasodilators are administered. Innervation of the peripheral vasculature is preserved, and changes in peripheral vascular resistance may still occur in response to alterations in sympathetic outflow from the vasomotor center due to signals from stretch receptors in the great vessels.

Drugs such as atropine, glycopyrrolate, neostigmine and pancuronium that act on the heart through vagal or sympathetic neuromechanisms will no longer affect HR. Alpha- and beta-adrenergic receptors remain intact and inotropes such as epinephrine and isoproterenol will cause appropriate responses from the heart.

The donor organ is subjected to ischemia–reperfusion injury and patients usually require inotropic support for separation from CPB. Left-ventricular diastolic dysfunction is common and characterized by a restrictive ventricular filling pattern, with a reduced preload reserve and a relatively fixed stroke volume. Sinoatrial node dysfunction is relatively common. Dopamine or isoproterenol are often selected and epicardial atrioventricular pacing can be instituted if necessary to achieve the desired HR. Temporary pacing wires are placed in all patients. Arrhythmias are quite common in the early postoperative period, usually premature atrial or premature ventricular contractions. Compression of intrathoracic structures may be problematic during closure of sternotomy, particularly if the donor heart is relatively oversized.

It is important to minimize PVR. Catecholamine release is reduced by ensuring the patient remains adequately anesthetized. Ventilation management is facilitated by muscle relaxants. Prior to separation from CPB, toilet of the airway should be performed and the lungs inflated with an inspiratory hold maneuver to eliminate atelectatic areas. Metabolic acidosis is corrected and a blood pH of 7.45–7.48 achieved by ventilating to moderate hypocapnia (30–32 mmHg) with 100% oxygen. Lung overdistension and positive end-expiratory pressure (PEEP) are avoided because PVR is lower when lung volumes are at functional residual capacity.

Elevated pulmonary artery pressures can be discerned by echocardiography and measured by the surgeon (catheter or palpation). Right ventricular failure may develop without manifesting increased pulmonary artery pressure because the “untrained” right ventricle may dilate and fail when posed with the increased work of high PVR. This situation can be recognized echocardiographically or with invasive monitoring: the CVP will rise as the left atrial pressure decreases and CO falls. Additional measures to control PVR may be necessary, including pulmonary vasodilator therapy such as nitric oxide, nitroglycerine, nitroprusside; and PGE1, prostacyclin, phosphodiesterase inhibitors, and isoproterenol. More extreme hypocapnia may help, but also causes cerebral vasoconstriction and leftward shift of the oxygen dissociation curve. If the patient’s CO remains inadequate despite maximal drug therapy, mechanical right ventricular assist or extracorporeal membrane oxygenation (EMCO) may be employed.

Blood loss during heart transplantation can be considerable and is associated with increased morbidity and mortality. Coagulation management is no different from that for other open heart surgeries in children (see Chapter 10).
Packed red blood cells are cytomegalovirus-matched, leukoreduced, and irradiated. For infants, some centers wash packed red blood cells to reduce the potassium load. Citrate-induced hypocalcemia impairs contractility and coagulation; this may be minimized by initiating a calcium infusion (calcium chloride 10–30 mg/kg/h). Rapid platelet transfusion may aggravate PVR.

Immunosuppression

Pediatric heart transplant provides a unique immunological opportunity because the development of the immune system extends not only into infancy, but continues throughout childhood. For example, cytokine production and the cytokine profile mature after birth. The absolute number of mature T cells and killer T cells is lower in the infant, naïve T cells are greater than in the adult, and the lymphocyte surface receptor repertoire is age-dependent. T-cell responses and phenotype are naïve, compared with adults, with decreased expression of integrins and adhesion molecules. Younger age at time of transplantation is associated with better long-term survival and lower frequency of rejection compared with older children. Infants apparently lacking significant anti-ABO antibody can safely undergo transplantation across ABO barriers, thus expanding the pool of donor hearts available to infants.

Immunosuppressive therapies can be categorized by their actions into: (i) broad spectrum immunosuppressants: corticosteroids; (ii) calcineurin inhibitors: cyclosporine and tacrolimus; (iii) antiproliferative agents: mycophenolate mofetil (MMF) and azathioprine; (iv) antibodies against interleukin-2: basiliximab and daclizumab; (v) target of rapamycin inhibitors: sirolimus; (vi) mono- and polyclonal T-cell antibodies: OKT3, antithymocyte gamma globulin (ATGAM), thymoglobulin; and (vii) non-drug therapies: total lymphoid irradiation, photopheresis and plasmapheresis.

Typical clinical use of these agents has been summarized as follows:

1 **Induction therapy:** Antibodies are used at the time of transplantation to reduce early rejection and diminish dose requirements for calcineurin inhibitors and corticosteroids. Data demonstrating improved survival are currently limited. T-cell-depleting antibodies include polyclonal rabbit antithymocyte globulin (thymoglobulin), equine ATGAM, and monoclonal murononab-CD3 (OKT3). The latter has neurologic effects, prominent first dose “cytokine release syndrome” and may increase the risk of lymphoproliferative disorders. Interleukin-2 blockers (basiliximab and daclizumab) are well tolerated.

2 **Maintenance therapy:** The choice and number of maintenance agents is largely guided by institutional experience and the recipient’s clinical profile, rejection history, and comorbid associations. The objective is to prevent acute and chronic rejection while minimizing the adverse effects of immunosuppression. All regimens involve a calcineurin inhibitor. Many patients receive adjunct therapy with an antiproliferative agent or sirolimus. Often, corticosteroids are also administered, although many programs attempt to limit or avoid their long-term use.

**Calcineurin inhibitors**

Cyclosporine (Sandimmune, Neoral) is the most commonly used immunosuppressant following pediatric heart transplantation. It binds to cyclophilin within the cytoplasm of T cells; this complex inhibits calcineurin phosphatase, thus interfering with the transcription of key cytokines required for T-cell activation and proliferation. Adverse effects may be dose related and include toxicity of renal, hepatic and neurologic systems, hypertension, hyperlipidemia, hirsutism, and gingival hyperplasia. Therapeutic drug monitoring is mandated because the therapeutic window is narrow and many other drugs influence drug levels. Cyclosporine trough levels are usually maintained in the range of 100–300 ng/mL.

Tacrolimus (Prograf, FK506) has a mode of action and spectrum of side effects that are very similar to cyclosporine. The choice of calcineurin inhibitor depends on institutional experience and drug side effects. Efficacy does not differ between the two agents but there may be less rejection (controversial) and fewer side effects with tacrolimus (no hirsutism or gingival hyperplasia, less hypertension).

Tacrolimus has been reported to allow more rapid weaning from corticosteroids. Like cyclosporine, the therapeutic window is narrow and blood levels can be affected by other medications. Trough levels are maintained in the range of 5–15 ng/mL.

**Antiproliferative agents**

Antiproliferative agents such as azathioprine (Imuran) and MMF inhibit lymphocyte proliferation and one of these agents is often added to calcineurin inhibitor therapy. Azathioprine is a purine antagonist that inhibits T and B cells. Bone marrow depression is common and dosing is guided by the white blood cell count. Mycophenolate mofetil (CellCept) converts to mycophenolic acid, an inhibitor of purine synthesis. Lymphocytes are suppressed because they lack a salvage pathway. Absorption is variable and dosing may be guided by blood levels. Gastrointestinal side effects rather than bone marrow depression are the usual dose-limiting factor.

**Sirolimus**

Sirolimus (rapamycin) is a macrolide antibiotic that blocks nuclear transcription of cytokines and can act synergistically with cyclosporine or tacrolimus. It is usually used to reduce calcineurin inhibitor dosing but its indications remain undefined. Sirolimus may inhibit the process of coronary
arteriopathy. Hyerlipidemia may occur and drug interactions are a concern.

Corticosteroids

Corticosteroids are non-specific anti-inflammatory agents that were widely used in the pre-cyclosporine era. Nowadays, they are used mainly as triple therapy (steroid + calcineurin inhibitor + antiproliferative agent or sirolimus). Many centers try to minimize the dose and duration of corticosteroid therapy. Side effects are myriad and include higher infection risk, diabetes mellitus, bone demineralization, and coronary artery disease. Rejection risk may increase when steroids are withdrawn.

Acute rejection therapy

High dose corticosteroid, usually methyl prednisolone, is first line therapy for acute rejection. Other agents are reserved for refractory or recurrent severe rejection and for rejection with severe hemodynamic compromise. These include monoclonal and polyclonal anti-T antibodies. Recurrent moderate rejection can usually be controlled with enhanced maintenance therapy (tacrolimus, sirolimus and corticosteroids).

Use of non-pharmacologic therapies for resistant or recurrent allograft rejection has been reported. Total lymphoid irradiation is given as an inverted Y-shaped mantle biweekly for 10 treatments. Bone marrow depression and development of lymphomas are concerns. Plasmapheresis is used to temporarily remove anti-donor antibodies in highly sensitized recipients. Photopheresis is a technique of immune modulation by reinfused lymphocytes from patients pretreated with psoralen and exposed to ultraviolet-A light \textit{ex vivo}. No experience in children is reported.

Chronic rejection therapy

Chronic rejection is manifest as coronary vasculopathy. There are no proven therapies that can halt or reverse this process and retransplantation is the most suitable option for advanced diffuse disease.

Outcome following heart transplantation

Data from the International Society for Heart and Lung Transplantation show the actuarial 10-year survival for all pediatric heart recipients exceeds 50% (Fig. 24.3). A Review of long-term survival of children who had undergone heart transplantation at Stanford showed, with the assumption of survival to 10 years, cumulative survival was 79% at 14 years and 53% at 20 years. Infants less than 1 year of age had a statistically lower 1-year survival than adolescents. This early infant mortality, usually within the first 30 days after transplantation, has decreased in recent years and is most likely from graft failure. Hemorrhage, infection and other causes only account for a small percentage of deaths. Once beyond the first year post-transplant, infants fare better than older children, perhaps reflecting the impact of immunologic aspects of development on transplant survival. Conditional 3-year actuarial survival was greater than 95% for infants and 80% for adolescents, and incremental yearly mortality between 4 and 10 years post-transplant was less than 2% for infants and 4% for adolescents.

Risk factors for 1-year mortality were (in order): CHD, mechanical ventilation at time of transplantation, non-cardiac disease, ventricular assist device, and donor cause of death; and for 5-year mortality were: history of previous transplant and inotropic support at time of transplantation. Acute rejection was the leading cause of death during the first 3 years post-transplant but was displaced thereafter by coronary artery vasculopathy, which accounted for 40% of all deaths beyond 3 years.

Rejection

Rejection is defined by the Pediatric Heart Transplant Study Group as the clinical decision to intensify immunosuppression in association with either histopathology or dysfunction. Pediatric heart transplant recipients experience an average of about two rejection episodes in the first 3 years after transplantation. Approximately one-third of patients are rejection-free. Rejection that occurs more than 2 years after transplantation has been linked to poor compliance with therapy. Acute cellular rejection is fatal in less than 10% of episodes. Clinical evidence of rejection ranges from no symptoms to tachycardia, tachypnea, lethargy, irritability, poor feeding, fever, hepatomegaly, new murmur, gallop rhythm, and supraventricular and ventricular tachycardia.
Endomyocardial biopsy remains the “gold standard” for the diagnosis of acute allograft rejection. The numbers of infiltrating lymphocytes and the presence of myocyte injury are used to grade rejection and to guide rejection therapy. A histologic classification system is used to grade the biopsy between 0 and 4. Current practice is to intensify immunosuppression if the biopsy score is 3 or greater. The use of echocardiography as a non-invasive method of diagnosing acute rejection is unresolved. Indices of systolic dysfunction report diastolic dysfunction as a non-invasive method of diagnosing acute rejection if the biopsy score is 3 or greater. The use of echocardiography as a non-invasive method of diagnosing acute rejection is unresolved. Indices of systolic dysfunction report diastolic dysfunction as a late finding. Diastolic dysfunction indices have high sensitivity but low specificity because diastolic parameters are load-dependent and abnormal in a significant number of recipients in the absence of rejection. Surveillance for late rejection is controversial. Some centers use clinical and echocardiographic parameters for screening and reserve endomyocardial biopsy for selected cases. Hyperacute rejection is a rare syndrome mediated by preformed recipient cytotoxic antibodies against donor heart antigens and leads to intractable heart failure and death unless mechanical support is instituted.

Graft atherosclerosis

The long-term decline in patient survival is primarily due to accelerated coronary vasculopathy involving intramyocardial and epicardial coronary arteries and veins. It is an immune-mediated disease and interacts with non-immune risk factors such as dyslipidemia and hypertension. The incidence of graft atherosclerosis is about 15% at 5 years post-transplant. Currently, there is no known treatment.

Infection

Infection is a significant cause of morbidity and mortality, particularly in the first 6 months after transplantation when immunosuppression is greater. The most common types of serious infection are bacterial (60%), cytomegalovirus (18%), other viral (13%), fungal (7%), and protozoal (2%). Bacterial, protozoal, and fungal infections commonly involve the respiratory tract or sternal wound. Viral infections increase the risk of graft rejection. Ebstein–Barr virus is associated with lymphoproliferative disease.

Malignancy

Although there is an increased risk of malignancy in children after heart transplantation, the risk is extremely low. The majority of these neoplasms are lymphoproliferative disorders that often respond to reduction in immunosuppression and are Epstein–Barr virus driven. When primary Epstein–Barr virus infection develops, antiviral therapy with acyclovir should be considered.

Other complications

Children with CHD who required extensive reconstruction of vessels during transplantation may develop stenoses at anastomotic sites (e.g., aorta, pulmonary veins). This can usually be relieved by interventional catheterization techniques but some cases may require surgery. Endomyocardial biopsy procedures should be minimized because there is some risk, including trauma to veins, tricuspid valve and heart muscle, air emboli, arrhythmia, and infection.

Quality of life

Approximately 50% of children do not require hospitalization in the first year after transplantation. By 3 years, this percentage had increased to 72%. Rejection and infection are the major causes for hospitalization. The functional status of survivors is excellent. The percentage of survivors without functional limitation was 93% at 1 year and 95% at 5 years. Less than 1% required total assistance. Pre-adolescent children exhibited “catch-up” growth in height and weight after transplantation, with a height mean at approximately the 40th percentile. Older children failed to demonstrate any increase in linear growth post-transplant but did increase in weight. Failure of linear growth is correlated with steroid requirements.

Over 90% of patients are discharged home after transplantation with good cardiac function (New York Heart Association class I). Ventricular growth is in proportion with growth of the recipient. Some hypertrophy of the muscle wall is common, but cardiac function is normal with high–normal end-diastolic pressures. Coronary autoregulation is normal. Pulmonary vascular resistance usually becomes normal but may remain elevated in some children with congenital heart defects. Pulmonary arteriovenous malformations regress after transplantation. Reduced exercise tolerance has been reported.

The cumulative incidence of post-transplant morbidities at 5 years for survivors of heart transplantation was: hypertension (60%), hyperlipidemia (17%), coronary vasculopathy (11%), renal dysfunction (6%), and diabetes mellitus (5%). Chronic hypertension was associated with steroid therapy. A retrospective analysis of 104 children who underwent heart transplantation noted serious gastrointestinal complications in 18% of patients (median post-transplant follow-up was 3 years). Complications included (in order) pancreatitis, choledocholithiasis, recurrent abdominal infection, malignancy, and intestinal pneumatosis. Half of the patients with complications required abdominal surgery.

A review of cognitive and psychological outcomes after pediatric heart transplantation found that children and adolescents generally functioned within the normal range on most measures of cognitive function post-transplant. However, a
complicated transplant course may place these recipients at increased risk for cognitive difficulties post-transplant. Approximately 20% of recipients experienced significant symptoms of psychological distress (e.g. anxiety, depression, behavior problems) during the first year after transplantation. There is evidence that children with CHD should be considered separately because those who have undergone surgical palliation or repair have significantly lower scores on IQ and achievement tests, delays in reaching motor milestones, and higher frequencies of learning disabilities, use of special services, and speech, language, and behavioral abnormalities when compared with a normative sample. A study of developmental outcomes of patients with HLHS after heart transplantation reported cognitive deficits and adaptive/behavioral abnormalities. Mean scores of cognitive ability were 1 standard deviation below expected values, and the median Full Scale IQ was 89. Interestingly, the test scores were remarkably similar to those published for patients with HLHS after the Fontan operation, despite differences between these treatment strategies in duration of hypoxemia, number of surgical procedures, and long-term medical management. The similarities in neurological outcome suggest that genetic factors, congenital brain abnormalities, and ischemia/reperfusion injury may be more important than the type of surgery performed. As an aside, post-traumatic stress disorder seems to be relatively common in parents of pediatric heart transplant recipients.

**Heterotopic and heart–lung transplantation**

Potential recipients with elevated fixed PVR may be eligible for heterotopic heart transplantation or heart–lung transplantation. Actuarial survival rates of 83% (1 year) and 66% (5 year) have been reported, however experience is limited. Heart–lung transplantation experience is also limited, but survival rates reported are 67% (1 year) and 41% (5 year), equivalent to those of adults.

**Retransplantation**

Retransplantation accounts for less than 5% of heart transplantations, despite the large number of infants who undergo transplantation and who potentially need retransplantation in the next decade. Indications for retransplantation are (in order) coronary vasculopathy, acute rejection, chronic rejection, and intraoperative graft failure. An ethical dilemma exists whether it is appropriate to use scarce donor organs for retransplantation when the long- and short-term outcomes are not as good as with other potential candidates.

**Anesthetic management of children who have undergone heart transplantation**

Patients may present for surgery because of complications from cardiac transplantation (e.g. infection, malignancy, drug adverse effects), or the indication for surgery may be unrelated to heart transplantation. Successful anesthetic management requires consideration of the patient’s medical status, the physiology of the transplanted heart, and the implications of immunotherapy. These have been discussed above.

**Future prospects**

Currently, heart transplantation cannot be regarded as a “cure.” While new immunosuppressive agents have been introduced in the last decade, progress on induction of graft tolerance remains at a relatively preliminary stage. Transplantation tolerance implies the patient will indefinitely accept their allograft but without the need for chronic immunosuppressive therapy. Such a state would leave the patient immunocompetent against all non-donor antigens and, thus, at no increased risk for infection or malignancy. Controversy exists on the best manner to monitor rejection. Controversy has also arisen as to the appropriateness of fetal listing for transplantation. Currently, fetuses can be placed on a waiting list for cardiac transplantation once they reach 36 weeks gestation. The debate about management of HLHS continues to evolve. Donor shortage remains a frustrating problem. The role of options such as a totally implantable pediatric artificial heart, xenotransplantation, clinical application of stem cell biology, and transplantation across ABO barriers remain frontiers in pediatric heart transplantation.

**Lung transplantation**

In the last decade, lung transplantation has been accepted as a treatment modality for adult patients with end-stage lung disease. In spite of concerns regarding growth of the implanted lungs, technical difficulties, and lack of well-defined indications, lessons from adult lung transplantation have been extended to children with end-stage lung disease. More than 600 such procedures have been performed around the world in patients below 18 years of age. This, however, represents less than 5% of the cumulative total of 14 000 lung transplantations reported by the registry of International Society of Heart and Lung Transplantation (ISHLT). Even though survival after lung transplantation in children approaches or may even exceed adult lung transplantation, occasionally it is still described as an “experimental” procedure. Since the inception of pediatric lung transplantation program in 1990, more than 260 such procedures have been performed at St Louis Children’s Hospital (SLCH).

These children undergo a number of surgical interventions before and after lung transplantation, thus it is important to be familiar with the anesthetic implications of end-stage lung diseases in childhood, conduct of lung transplant surgery, and management of a child after lung transplantation.
Donor pool

Donor availability remains a major obstacle to expanding the indications and viability of lung transplantation as a treatment modality for a vast list of childhood diseases causing irreversible lung damage. After an initial increase, the number of pediatric lung transplants performed each year has remained constant. This observation has been made by most of the institutions offering pediatric lung transplant surgery. Longer waiting lists with an ever-increasing number of children suggest that this plateau is caused by lack of potential donors. The average time from listing to transplantation at SLCH currently stands at an average of 225 days (range 1–1484). Approximately one third of the children on the waiting list die before transplantation. According to the data from US Department of Health and Human Services, there are more donors (> 15% of total donors) under the age of 18 years than recipients (< 5% of total recipients). It suggests that some of the lungs from donors under the age of 18 years are being used for adult patients. As the outcome from pediatric lung transplantation improves, the list of indications is expected to expand. This will further increase the time a child has to wait before receiving matching donor lungs. Current criteria for donor selection are listed in Table 24.2. These criteria are used with reasonable flexibility.

Various strategies are being evaluated to increase the size of the potential donor pool. Aggressive measures such as improving ventilation and treatment with diuretics may improve gas exchange of otherwise borderline donor candidates. Starznicka and colleagues studied survival in lung transplant recipients from borderline donors who had been aggressively treated with steroids, diuretics, inotropes, fluid restriction, and central venous pressure monitoring. Survival at 30 days and 1 year after surgery was no different from patients receiving lungs from donors who met standard criteria. Currently ischemic times of 6–8 hours are considered acceptable for donor lungs. Better understanding of the mechanisms of ischemia and reperfusion injury may lead to improvement of preservation techniques, longer acceptable ischemic times, and retrieval of potential donors from longer distances. Clinically it appears that methods like infusion of donor lungs with prostaglandins and the use of better preservative solution have reduced the incidence of acute graft failure.

The technique of transplanting mature lobes from two voluntary living related donors has been used in children. As morbidity accompanying donor lobectomy is significant, this option is often reserved for critically ill children with little chance of surviving until cadaveric lungs become available. The need for retransplantation is also considered an indication for living related lung transplantation. Since the availability of cadaveric lungs is unpredictable, some institutions offer living related lung transplantation as a primary procedure.

Recently, following successful animal experiments, Steen et al. successfully transplanted lungs from a non-heart beating donor. The impact of these strategies on long-term survival, early graft dysfunction, and incidence of bronchiolitis obliterans (BO) is still not known. Until the supply of donor lungs increases, a significant number of children will continue to die while waiting for lung transplantation.

### Indications, contraindications and listing criteria for lung transplantation

Pediatric lung transplant recipients consist of a heterogeneous mix of age groups and disease diagnoses. Data from registry of ISHLT indicate that most pediatric lung transplant recipients are between 11 and 17 years of age with a second smaller group of children less than 2 years of age. This distinction is significant as the disease profile and physical status at the time of transplantation is remarkably different between the two groups. Indications for lung transplantation are listed in Table 24.3.

Cystic fibrosis and pulmonary hypertension remain the most frequent indications for lung transplantation in older children. Infant recipients are usually full-term babies, presenting with respiratory distress that rapidly progresses to end-stage pulmonary failure, secondary to a variety of rare diseases such as surfactant B deficiency, primary alveolar proteinosis, and pulmonary vascular disease. Unlike older recipients who present with chronic pulmonary insufficiency and minimal oxygen supplementation, most of the infant

### Table 24.2 Selection criteria for pediatric lung transplantation donors.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO blood group compatibility</td>
<td>100 (100%)</td>
</tr>
<tr>
<td>Reasonable size match</td>
<td></td>
</tr>
<tr>
<td>HIV negative serology</td>
<td></td>
</tr>
<tr>
<td>Less than 55 years of age</td>
<td></td>
</tr>
<tr>
<td>PaO₂ &gt; 300 mmHg at an FiO₂ 1.0</td>
<td></td>
</tr>
<tr>
<td>No active pulmonary infection</td>
<td></td>
</tr>
</tbody>
</table>

HIV, human immunodeficiency virus.

### Table 24.3 Common indications for lung transplantation in children.

<table>
<thead>
<tr>
<th>Pre-transplant diagnosis</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic fibrosis</td>
<td>89 (42%)</td>
</tr>
<tr>
<td>Pulmonary vascular disease</td>
<td>44 (21%)</td>
</tr>
<tr>
<td>Bronchiolitis obliterans</td>
<td>21 (10%)</td>
</tr>
<tr>
<td>Primary alveolar proteinosis</td>
<td>12 (6%)</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>15 (7%)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>26 (12%)</td>
</tr>
</tbody>
</table>

candidates at SLCH were mechanically ventilated with a significant number on ECMO at the time of surgery. Lung transplantation is still considered a palliative surgery but an increasingly large number of children are listed for repeat transplantation as a treatment option for terminal BO.

The criteria for listing patients for lung transplantation are based on the natural history of the disease, functional status, hemodynamic parameters, and overall medical judgment. The generally acceptable principle is that children should be listed when they have less than a 50% chance of surviving for another 2 years. However, the natural history of rare diseases leading to end-stage respiratory failure may not be fully understood. In a retrospective analysis by Kerem et al., cystic fibrosis patients with forced expiratory volume in first second (FEV₁) of less than 30%, Pao₂ of less than 55 mmHg, or a Paco₂ of greater than 50 mmHg, were observed to have more than 50% mortality in 2 years, which is the average time a cystic fibrosis patient waits before lung transplant surgery. Patients with pulmonary hypertension usually deteriorate rapidly.

Most centers consider patients infected or colonized with panresistant bacteria like Burkholderia cepacia as an absolute contraindication. Children with coexisting severe hepatic and renal dysfunction, family history of poor medical compliance, or severe psychiatric ailments are also not usually considered for this surgery. Many children with cystic fibrosis have significant hepatic dysfunction. These patients can be candidates for simultaneous lung and liver transplants. Combined simultaneous liver and lung transplantation have been carried out successfully in five cystic fibrosis patients at SLCH.

**Use of cardiopulmonary bypass**

Use of CPB is an issue of much debate in adult lung transplant surgery. Unlike the surgical technique in adults, most pediatric lung transplant surgeries are carried out with the assistance of CPB. There are several reasons for using CPB in children. In children with cystic fibrosis, risk of cross contamination is minimized by simultaneous removal of both native lungs. Most children are physically too small to accommodate a double lumen endotracheal tube. Pediatric patients with severe pulmonary hypertension and infants are often too unstable to tolerate one-lung ventilation. Cardiopulmonary bypass also assists in improving surgical exposure by providing stable hemodynamics. Consequently use of CPB greatly simplifies anesthetic and surgical management and helps to minimize ischemic times of donor lungs.

Use of CPB, however, comes with its own risks and potential for complications. Generation of inflammatory mediators and activation of complement cascade may contribute to ischemic-reperfusion injury of the donor lungs. Systemic anticoagulation may increase intraoperative bleeding and accrue the need for blood products. The data from adult patients suggest a higher incidence of graft dysfunction associated with use of CPB. This observation may reflect the fact that CPB was more often used in patients with pulmonary hypertension, a pre-transplant diagnosis associated with higher mortality. Moreover in children, early as well as long-term survival after lung transplantation is either similar to or better than those in adults suggesting a minimal impact of CPB on the outcome.

**Surgical technique**

Pediatric lung transplantation is performed using a bilateral anterolateral trans-sternal clamshell incision. Though single lung transplantation has been performed in a few patients, most children undergo bilateral sequential lung transplantation. Maximal exposure and dissection is carried out before instituting CPB. Lung transplant is initiated by performing end-to-end bronchial anastomosis. Since the bronchial circulation is not reestablished, peribronchial tissue is wrapped around the anastomotic suture line. This measure is considered sufficient to ensure adequate blood supply to an otherwise ischemic tissue. This is followed by anastomosis of pulmonary artery. The donor atrial cuff is attached to the recipient’s left atrium to avoid individual pulmonary vein anastomoses, reducing the risk of a potentially serious complication of pulmonary vein stenosis. Smaller donor lungs can expand to fill a relatively large recipient chest cavity. In case donor lungs are too large, volume reduction has to be carried out in order to remove areas of atelectasis.

**Preoperative evaluation**

Children listed for lung transplantation at SLCH visit the preoperative anesthesia clinic and undergo an extensive evaluation, including ECG, echocardiogram, PFTs, arterial blood gas analysis, and complete metabolic panel. Children with pulmonary hypertension and associated cardiac defects are also subjected to cardiac catheterization, where PVR and its response to 100% oxygen or nitric oxide right ventricular function are evaluated, and cardiac anatomy is defined.

Children are at various degrees of end-stage respiratory failure at the time of transplantation. A large number of children, especially cystic fibrosis patients, are living at home with minimal oxygen supplementation. On the other hand, infants and small children are critically ill at the time of surgery. Almost all of the infants we have transplanted required mechanical ventilation or may be supported on ECMO.

When the notification of a potential donor arrives, the time until surgery is often short. Anesthesiologists are usually required to evaluate, anesthetize, and obtain adequate vascular access in these critically sick patients in a short period of time. There is evidence to suggest that longer ischemic time may correlate with increased incidence of BO.
Most children and parents carry a hospital given pager and have been anticipating the transplant for a long period of time. They are often excited and frightened at the same time. Anxiolytics such as midazolam can be safely given to most patients either orally or intravenously. However, one must be cautious in administering sedatives to patients with severe pulmonary hypertension without adequate hemodynamic monitoring. In children with Eisenmenger’s complex, intravenous or intramuscular ketamine is a reasonable choice as a premedicant.

Anesthetic management

Standard NPO guidelines are followed to minimize the risk of aspiration and contamination of new lungs. The choice of induction agent and muscle relaxants is largely guided by the patient’s condition. Propofol and etomidate are safe in patients with cystic fibrosis but ketamine may be preferred in patients with Eisenmenger’s complex and those with pulmonary hypertension. Unlike its effects in adults, ketamine does not cause a significant increase in PVR.63

Anesthesia is maintained with opioids like fentanyl and benzodiazepines, and can be supplemented with inhalational agents like isoflurane if permitted by the hemodynamics of the child.

Anesthesiologists must ensure that non-anesthetic drugs, including preoperative antibiotics and immunosuppressants, are administered on time. Some patients require continuous delivery of prostacyclin, a pulmonary vasodilator, which must be maintained. Prostacyclin must be administered through a separate lumen and should be given through a central line, as it tends to precipitate when given in combination with other drugs.

Since pediatric lung transplant surgery is carried out with assistance of CPB, patients are intubated with standard endotracheal tubes. The extensive nature of surgery and use of CPB mandates invasive monitoring of arterial and central venous pressure in all patients. Intraoperative and postoperative monitoring of pulmonary artery pressures is most beneficial in patients with primary or secondary pulmonary hypertension. The pulmonary artery catheter is advanced from the superior vena cava into the pulmonary artery. In smaller children, the surgeons can place a catheter directly into the pulmonary artery under direct vision. Intraoperative TEE provides valuable information about right ventricular function, post-bypass pulmonary artery pressures, and residual cardiac defects.64 Intraoperative TEE can be used to evaluate flow patterns in the pulmonary artery and pulmonary veins to rule out any stenosis.

Repeated suctioning of the endotracheal tube is required to effectively ventilate cystic fibrosis patients. Maintaining adequate gas exchange and oxygenation in the pre-bypass period is a challenge for the anesthesiologist. High $P_{\text{aco}}$2 (high 60s) values are common and permissive hypercapnia and mild respiratory acidosis is acceptable. Overzealous correction of hypercapnia, particularly during CPB, can lead to significant respiratory alkalosis and reduced cerebral blood flow that may produce to cerebral ischemia. A normal pH with elevated $P_{\text{co}}$2 should therefore be maintained through the entire intraoperative period.

Perioperative bleeding is a common and serious problem. Dense lung adhesions develop from previous chest surgeries and are often seen in cystic fibrosis patients; the dissection is time consuming and involves significant blood loss. Aorto-pulmonary collaterals are common in patients with chronic hypoxemia and contribute to bleeding in the pre-bypass period. Aprotinin, a serine protease inhibitor is routinely used to decrease perioperative bleeding in most institutions. In a retrospective review, Spray28 observed that the use of aprotinin is beneficial in reducing bleeding in children with a history of previous thoracotomy and those undergoing repeat sternotomy. Aprotinin also has the potential advantage of reducing the production of inflammatory mediators responsible for reperfusion injury; however, its impact on early graft function has not been evaluated. Repeat use of aprotinin carries a small but definite risk of anaphylactic reaction. Incidence of anaphylactic reaction after repeat dose has been reported to be low in pediatric patients (1.2%) compared to adult patients (6%). Also, the incidence of adverse reactions to repeat dose of aprotinin is higher when the re-exposure interval is less than 200 days.65

During CPB, the patient is usually cooled to 32°C. Cardioplegic arrest of heart and aortic cross-clamp is required in patients who require simultaneous intracardiac repair. All cystic fibrosis patients are colonized with bacteria and, after excision of both native lungs, the tracheal stump is irrigated with concentrated tobramycin to reduce contamination of donor lungs. After the first lung is implanted, a small amount of blood is allowed to eject into the pulmonary artery while the second lung is being anastomosed. This maneuver reduces the ischemic times for the first lung. At the conclusion of all the anastomoses, before weaning from CPB, ventilation is resumed. In most children, minimal inotropic support is needed to wean the patient off CPB. In children with pulmonary hypertension and those who undergo simultaneous repair of congenital heart defects, more than one inotropic drug is often required to improve myocardial contractility. Careful adjustment in tidal volumes and airway pressure are necessary to remove all visible atelecatic areas. A flexible bronchoscopy may be done to rule out any narrowing at the site of bronchial anastomosis and to evaluate any airway leak, which should be immediately repaired.

Primary graft failure

Persistent hypoxemia after weaning from CPB often signals the onset of acute graft dysfunction. Unlike other organs, vascular endothelium makes up a vast portion of lung
parenchyma, and oxygen is readily available to the metabolically active endothelium, producing free radicals both during reperfusion as well as during the ischemic phase. Inflammatory mediators like tumor necrosis factor, interleukins, and platelet-activating factors generated during preservation can trigger a cascade of events leading to increased permeability and movement of fluid into interstitial as well as alveolar space. Clinically, reperfusion injury presents as hypoxemia despite adequate ventilation and the production of pink frothy secretions from the endotracheal tube. Before attributing low PaO2 values to ischemic reperfusion injury, other reversible causes such as inadequate ventilation, right ventricular dysfunction with paradoxical right to left shunting, and atelectasis, must be ruled out.

In an effort to reduce reperfusion injury, PGE1 infusion at 0.025 µg/kg/minute is routinely started before establishing circulation to the first lung and is continued for 48 hours after the surgery. Prophylactic use of nitric oxide to prevent reperfusion injury remains controversial. Nitric oxide is a potent smooth muscle relaxant in vascular muscle cells. In a small group of adult patients, Thabut et al.67 were able to demonstrate a marked decrease in the incidence of allograft dysfunction with the prophylactic administration of nitric oxide and pentoxifylline. In this study, prophylactic nitric oxide–pentoxifylline significantly improved hemodynamics and reduced the duration of postoperative mechanical ventilation as well as early mortality. In another prospective study in adult patients, Ardehali et al.95 concluded that prophylactic inhaled nitric oxide improved gas exchange and reduced pulmonary arterial pressures in all patients including those with established reperfusion injury. Prophylactic administration of nitric oxide, however, did not reduce the incidence of reperfusion injury. Nitric oxide is expensive and is associated with platelet dysfunction, bleeding and methemoglobinemia. Currently prophylactic use of nitric oxide to reduce the incidence of acute graft dysfunction is not indicated until further studies establish its role. Other pulmonary vasodilators such as inhaled prostacyclin (Iloprost) have been shown to be efficacious and safe for treatment of severe pulmonary hypertension. Some patients with severe reperfusion injury and high pulmonary pressures are not responsive to nitric oxide and require ECMO support to allow recovery of donor lungs.

Postoperative course

The postoperative course and duration of stay in intensive care varies by age group and by pre-transplant diagnosis. Older children with cystic fibrosis require mechanical ventilation for an average of 3 (1–47) days and their average stay in the intensive care unit is 5 (1–53) days. On the other hand, infants and smaller children require prolonged mechanical ventilation (24 ± 19 days) and a longer intensive care unit stay (56 ± 33 days). This difference in their postoperative course can be explained by small size, poor preoperative status, airway complications, and associated cardiac defects. Children with pre-transplant diagnosis of pulmonary hypertension manifest significant hemodynamic instability in the immediate postoperative period, are kept sedated and paralyzed for the first 48 hours after the surgery.

In the immediate postoperative period, pain relief is accomplished by narcotic infusions and patient-controlled analgesia. Regional analgesia with an epidural catheter has been frequently used in adult patients but systemic heparinization required for CPB and the emergent nature of surgery add difficulty to the preoperative placement of an epidural in pediatric patients. Many small children require mechanical ventilation and sedation for a period lasting more than 72 hours. Post-surgical placement of an epidural catheter in these younger patients is of minimal value. Epidural analgesia on the day before the surgery may be planned for older children undergoing elective living related donor transplantation. Older patients who may be extubated within 12–24 hours may be candidates for preoperative placement of a thoracic epidural catheter, or in the immediate postoperative period. Careful attention to the coagulation status and the risk–benefit ratio with systemic heparinization must be considered.

Surveillance

These children are monitored very closely for infection, rejection and the development of BO. Pulmonary function tests are performed at regular intervals to monitor function and growth of transplanted lungs. Older children can easily perform spirometric tests such as FEV1, forced vital capacity (FVC), and flow volume loops. Since standard PFTs require the patient’s cooperation, these tests cannot be performed in infants and younger children. Instead, expiratory flow rates at functional residual capacity are measured by applying rapid thoraco-abdominal compressions at the end expiration. Any deterioration in these values is further investigated by invasive tests such as bronchoscopies, lung biopsy, computed tomography (CT) scan, and open lung biopsy.

Changes in transplanted lungs

Physiological changes

Transplantation surgery produces denervation of donor lungs, producing only minimal consequences on airway reflexes, mucociliary movement, and bronchial hyperactivity. Denervation also leads to the loss of afferent stimuli to the respiratory center; and loss of coordination between thoracic and abdominal respiratory muscles is sometimes obvious in the immediate postoperative period. Adult lung transplant patients have a subnormal carbon dioxide response curve, and increased sympathetic and reduced parasympathetic activity. Loss of lymphatics in transplanted lungs makes...
them more susceptible to pulmonary edema in the initial post-operative period, and increased vasculature and water content result in lower compliance.75

**Growth of transplanted lungs**

Somatic growth in lung transplant recipients lags behind normal children, with height and weight staying between the fifth and tenth percentiles. However, based on PFTs, radiological and histological evidence, it appears that lungs continue to grow after transplantation. Cohen et al.76 showed that increases in functional reserve capacity accompanying somatic growth, which is comparable to normal subjects. This simultaneous increase in functional reserve capacity and \( FEV_1 \) suggests an increase in number of alveoli rather than overdistension of the alveoli. Histological studies have supported the assumption that number of alveoli increase after transplantation of immature cadaveric lungs. Transplanted mature lobes of living related donors also continue to grow. These lobes are able to accommodate the entire \( CO \) without an increase in pulmonary artery pressures suggesting growth in the pulmonary vasculature. On postoperative chest radiograph, transplanted mature lobes expand and fill the entire chest cavities. Morphometric studies suggest that this increase is a result of distension of alveoli rather than an increase in number of alveoli.77 The growth of larger airways is also suggested by the ability to tolerate larger flexible bronchoscopes with the passage of time. Ro et al.78 using CT imaging in a small group of patients were able to demonstrate near normal growth pattern in the trachea and both donor and native segments of bronchi.

**Airway complications**

Dehiscence of the bronchial anastomosis is rarely seen today. However, bronchial stenosis and tracheomalacia still develop frequently in adult as well as pediatric lung transplant recipients. Huddleston et al.55 reported 16% incidence of airway stenosis in patients less than 18 years of age, an incidence similar to that reported in adults. The underlying mechanism of airway stenosis is thought to be relative ischemia at the bronchial anastomosis. Other factors like high doses of corticosteroids and frequent infection also contribute to the development of airway stenosis. Usually airway complications are diagnosed within the first month after transplant. Initial treatment of stenosis at the bronchial anastomosis involves repeated balloon dilation using a rigid bronchoscope under fluoroscopic guidance. Mechanical stents are placed across the anastomotic site. Cardiac catheterization with angiography can confirm the diagnosis and a mechanical stent can be placed if a significant pressure gradient is measured across the anastomotic site.

**Vascular complications**

Vascular complications are rare, and most commonly mechanical obstruction to blood flow develops from redundant tissue of the pulmonary artery or the left atrial cuff. Stenosis of either pulmonary artery or pulmonary vein usually manifests with symptoms similar to those of reperfusion injury, such as increased pulmonary artery pressures with pink frothy secretions and hypoxemia. Pulmonary artery or vein stenosis can be diagnosed with intraoperative TEE, and all patients undergo a routine lung perfusion scan within the first 24 hours as a screening tool. Cardiac catheterization with angiography can confirm the diagnosis and a mechanical stent can be placed if a significant pressure gradient is measured across the anastomotic site.

**Nerve injuries**

Injury to the phrenic, recurrent laryngeal and vagus nerves are common after lung as well as heart and lung transplant surgery. Huddleston59 reported a 22% incidence of phrenic nerve injury in children, and the resulting diaphragmatic paralysis is a transient phenomenon but can prolong the need for mechanical ventilation and postoperative intensive care. Injury to the vagus nerve leads to gastroparesis and gastroesophageal reflux. In a small retrospective study, delayed gastric emptying times were reported in 83% of adult patients following combined heart and lung transplantation.81 Severe gastroparesis affects absorption of immunosuppressant drugs. Delayed gastric emptying may also predispose these patients to silent aspiration of gastric contents resulting in recurrent pneumonia. The incidence of severe gastroesophageal reflux is as high as 50% after lung transplantation. Infants are especially susceptible and most of them require surgical interventions such as Nissen fundoplication. Injury to the recurrent laryngeal nerves leading to vocal cord paralysis is seen in 10% of children, most commonly affecting the left vocal cord, and most recover.79

**Medical complications**

**Graft rejection**

Recurrent graft rejections are common after lung transplantation. Rejection tends to occur less frequently in infants compared to older children and adults. This discrepancy may be explained by their relatively immature immune system.71,82 The clinical picture of rejection is usually non-specific, and therefore any deterioration in clinical status or PFT measurements are investigated with a lung biopsy to rule out acute
rejection. Such episodes are aggressively treated with intravenous methylprednisolone followed by newer immunosuppressant drugs such as antithymocyte globulin, tacrolimus, and MMF.

Immunosuppression, abnormal mucociliary movement in transplanted lungs, and frequent hospitalizations contribute towards an increased risk of serious infections. Prophylactic antibiotics and antifungal medications are routinely given to these patients.

**Bronchiolitis obliterans**

Bronchiolitis obliterans remains the Achilles heel of lung transplantation. The histological features of BO include scar formation and fibrosis of small airways with thickening of blood vessels. Clinically, BO presents as progressive deterioration of airflow and limitation in activity. The FEV₁ is a reliable indicator of graft function, and BO is diagnosed by a greater than 20% deterioration from the previous values of FEV₁. The overall incidence remains about 50% at 5 years. Prolonged ischemic time, age more than 3 years, and more than two episodes of rejection have been identified as risk factors for developing BO in children. The incidence of BO was only 20% in patients with ischemic time of less than 2 hours compared to 52% incidence seen in patients where ischemic time was more than 6 hours. Three patients receiving mature donor lobes were perceived to be immune to developing BO. This observation may, however, reflect the shorter ischemic times seen during living related lung transplantation. The incidence of BO also seems to be low in infants, probably because they have lower incidence of rejection. Infants had an average of 0.2 episodes of acute rejection. This is significantly lower when compared to older children who had an average of 1.95 rejection episodes. Other factors like pre-transplant diagnosis, early graft dysfunction, and presence of cytomegalovirus do not affect incidence of BO. Retransplantation remains the only option for children with BO resulting in severe pulmonary insufficiency.

**Side effects from immunosuppressive drugs**

Lung tissue is more susceptible to graft rejection than other organs because of a large endothelial surface and the presence of large number of immunologically active cells. Therefore immunosuppressive drugs are used in higher doses and for a longer duration after lung transplant surgery. Most lung transplant centers use a triple drug (cyclosporine, azathioprine, and steroids) regimen. Each drug used in this combination may have multiple side effects and toxicities. Cyclosporine plasma levels must be closely monitored in cystic fibrosis patients due to unreliable absorption and variable hepatic clearance. In fact, an increased incidence of central nervous system complications like seizure, headache, and stroke in cystic fibrosis patients has been attributed to high plasma levels of cyclosporine. More than one third of children develop hypertension at 1 year after lung transplantation due to immunosuppressive therapy, and this number increases to 71% after 5 years. A significant number of patients develop chronic renal insufficiency occasionally requiring renal transplantation.

A number of malignancies including post-transplant lymphoproliferative disease (PTLD) and hepatic sarcoma have been reported in lung transplant recipients. The greatest risk factor for PTLD is a pre-transplant diagnosis of cystic fibrosis. In patients with cystic fibrosis, the only risk factor associated with PTLD was two or more episodes of acute rejection within 3 months after transplantation.

**Intestinal obstruction**

The incidence of intestinal obstruction is high after lung transplantation in children with cystic fibrosis. A significant number of children undergo laparotomy for procedures like gastrostomy, jejunostomy, and meconium ileus. In one series, 10% of patients required laparotomy for bowel obstruction after lung transplantation. Previous laparotomy is identified as a risk factor.

**Arrhythmias**

The left atrial suture line is a potential source of abnormal depolarization and repolarization. Clinically significant atrial flutter is seen in 11% of pediatric lung recipients. In most cases arrhythmias are persistent and require treatment with antiarrhythmic drugs like procainamide and amiodarone.

**Mortality and long-term survival**

The overall first year survival rate is reported to be 77%. Survival declines to 63% at 3 years, and only 54% are alive at 5 years after transplantation. Primary graft failure is the leading cause of early mortality accounting for 62% of deaths. Infants also have very high (25%) early mortality. Bronchiolitis obliterans, infection, and malignancies are the leading causes of death in the late period. Patients with pre-transplant diagnoses such as pulmonary hypertension and repeat transplant surgery appear to have relatively poor outcome.

**Summary**

Lung transplantation has become a viable option to prolong life in children with end-stage lung disease. A large number of children still die prematurely because of lack of suitable donor organs. Improving techniques of organ preservation may help reduce the incidence of fatal complications like primary graft failure and BO.
References


