In the past 25 years, cardiac transplantation has become the standard of care for children with end-stage cardiomyopathy and congenital heart disease. Advances in medical therapy and peri-operative management have resulted in excellent medium-term survival rates.

Paediatric registry data from the International Society for Heart and Lung Transplantation (ISHLT) indicate that between 1982 and 2005 almost 7,000 heart transplants were undertaken. The current figure is approximately 400 transplants per year, distributed among 82 centres. Almost 45% of transplantations now occur at a centre performing an average of more than 10 each year.

This report discusses the current status of cardiac transplantation in children.

**Indications**

Typical indications for heart transplantation in children include the following:

- intractable symptomatic heart failure (New York Heart Association (NYHA) Class III-IV);
- need for permanent mechanical cardiac support;
- frequent repeated discharges from an implanted automatic implantable cardioverter defibrillator device; and
- poor quality of life in patients with uncorrectable cyanotic heart disease.

Usual exclusion criteria include the following:

- active malignancy;
- irreversible dysfunction of other organs (combined organ transplant may be a consideration [e.g. heart and lung or heart and kidney]);
- irreversible degeneration/damage of other organ systems that precludes rehabilitation after heart transplantation;
- uncontrolled infection;
- inability to comply with complex medical therapy, e.g. due to chronic cognitive or neuropsychiatric deficits in the absence of a carer taking on this role; and
- active substance abuse, including smoking, alcohol and illicit drug use.

Although transplantation is a very effective treatment for advanced heart disease, the long-term results are limited by chronic rejection and the non-cardiac sequelae of long-term immune suppression. Specific paediatric considerations that do not preclude transplantation but may have an impact on long-term outcomes include the presence of developmental and intellectual deficits, genetic syndromes and extracardiac malformations. The paediatric population also includes an increasing number of older individuals with palliated congenital heart disease who present their own unique challenges.

**Pre-transplant Assessment**

Pre-transplant assessment is geared towards evaluation of the patient’s suitability and need for cardiac transplantation, as well as his or her family and social conditions. At the same time it provides the patient and family with sufficient information to allow them to make an informed decision about whether they would like to proceed. The assessment usually takes place over a period of days to weeks and is not complete until everyone involved has a full understanding of the potential risks and benefits of transplantation for the particular patient.

A complete history and physical examination establish symptoms and physical findings. An assessment of arrhythmic potential is usually based on the underlying disease, symptoms and results of Holter ECG recording. Many children being considered for transplantation are unable to perform a formal exercise test, but a six-minute walk with monitoring of transcutaneous oximetry can give an indication of exercise capacity. Cardiac investigations are directed towards confirming the aetiology (in the case of cardiomyopathy) and anatomical diagnosis (in the case of congenital heart disease). Cardiac systolic and diastolic function should be fully quantified. Typically, this includes assessment of the systemic ventricular ejection fraction, tissue Doppler (if available) and evaluation for possible dysynchrony. Cardiac catheterisation and angiography may be helpful in outlining post-surgical anatomy; haemodynamics, including cardiac output and pulmonary vascular resistance; and the presence of acquired collateral vessels, which may complicate the post-transplant period. Hepatic, renal and neurological function should be explored, and specific imaging may be required if there is evidence of specific organ dysfunction. Serology is undertaken to assess exposure to viruses, including cytomegalovirus (CMV), Epstein-Barr virus (EBV) and HIV, and to check hepatitis B and C status. Blood grouping, tissue typing and panel reactive antibody levels are also performed to permit prospective B and T
cell matching with potential donors. Routine vaccines, including chickenpox, should be completed if transplantation is not considered urgent. The transverse and oblique cardiac dimensions are measured on a chest radiograph to aid determination of suitable donor size.

Alternatives to Transplantation

Medical Therapy
There are few available data about the efficacy of medical therapy for the treatment of heart failure in children. Most currently used therapies have been extrapolated from usage in adults. The ISHLT guidelines for management of heart failure in children include the use of diuretics, angiotensin-converting enzyme inhibition, digoxin and β-adrenoceptor blockade.1 The use of carvedilol in patients with cardiomyopathy is widespread, despite a lack of convincing evidence of its benefit.2 Many patients on optimal combination medical therapy will improve sufficiently to delay or avoid transplantation. The decision about when to consider cardiac transplantation in children with cardiomyopathy is best made by a paediatric cardiologist with expertise in the management of cardiomyopathy and end-stage congenital heart disease.

Implantable Cardioverter–Defibrillators
Some children are at greatest risk of sudden death rather than progressive congestive heart failure and may benefit from an implantable cardioverter–defibrillator (ICD). Despite an increased rate of complications such as lead fractures and inappropriate shocks in children, ICDs are a suitable alternative to transplantation for some children.3

Cardiac Resynchronisation Therapy
Another emerging strategy for children with advanced cardiac dysfunction is cardiac resynchronisation therapy (CRT). CRT may have substantial haemodynamic benefits in patients with intraventricular electrical conduction delay (dysynchrony) and ventricular dysfunction, including patients with varying forms of congenital heart disease. Patients treated successfully may improve enough to avoid or defer consideration of transplantation.4

Palliation for Hypoplastic Left Heart Syndrome
The optimal treatment for hypoplastic left heart syndrome (HLHS) continues to be debated. The principal options involve either primary cardiac transplantation or staged reconstructive surgery beginning with a modified Norwood procedure. The major disadvantage of transplantation for children with HLHS is the low availability of suitable donors within the required time-frame. The Pediatric Heart Transplant Study Group recently reported that of 262 infants with unpailliated HLHS listed for transplantation between 1993 and 1998, 25% died before a donor became available, and only 54% were alive at five years.5 In an overlapping era (1989–1994), survival rates for transplantation were 80–90% in experienced hands.7,8 It has been suggested that transplantation is the optimal choice if a donor is available within one month,9 but this applies to only a minority of centres.2

Donor Selection
Potential donors should be ABO blood-type compatible with the recipient and should have approximately the same cardiac size. ABO-incompatible donors may be used in the first year of life but may require augmented immune suppression, and long-term outcomes for mismatched transplants are as yet unclear. Donors up to three times the bodyweight of the recipient can be used if the recipient has considerable cardiomegaly. A modified bicaval technique, in which a small cuff of left-atrial tissue is left in place to avoid pulmonary venous anastomoses.12

Surgical Considerations
Around half of children one to 10 years of age who receive cardiac transplantation have underlying cardiomyopathy, and the majority of the rest have congenital heart disease.3,10 Recipients may have undergone multiple prior surgical procedures and there may be a requirement for special anatomical knowledge and reconstruction at the time of surgery. Complex anatomy, additional reconstructive surgery and acquired collateral vessels may lead to longer bypass time, graft ischaemic times and post-surgical bleeding.

In children in whom the anatomy is straightforward there are two main surgical approaches commonly used: either biatrial anastomoses,11 which avoids individual systemic and pulmonary venous anastomoses, or the bicaval technique, in which a small cuff of left-atrial tissue is left in place to avoid pulmonary venous anastomoses.12
Transplantation

Elevated pulmonary vascular resistance in the transplant recipient may lead to acute right-heart failure after transplantation. This may be difficult to recognise if the donor is unable to maintain normal cardiac output by generating a sufficiently high pulmonary artery pressure. The pre-transplant assessment should establish whether there is acute reactivity present in response to vasodilator therapy such as inhaled nitric oxide or intravenous prostacycline. Post-transplant remodelling ensures that the pulmonary vascular resistance is often no more than mildly elevated late after transplantation.

Bridges to Transplantation

In recent years, advances in the treatment of heart failure in children have modified the spectrum of children being considered for heart transplantation. Mechanical support is now widely used as a bridge to transplantation for children with circulatory collapse who would otherwise die before a suitable donor became available. In adults the use of mechanical support allows rehabilitation and reversal of end-organ dysfunction prior to being listed for cardiac transplantation. Children who are placed on mechanical support are often listed for transplantation shortly afterwards, accepting that rehabilitation may occur after transplantation. Some centres in Europe and North America report success with bridging to transplantation with extra-corporeal membrane oxygenation (ECMO). However, ECMO is best employed when the likely waiting time is less than four weeks, due to complications of bleeding, sepsis and dysfunction of other organs. Baziv et al. report 46 paediatric patients bridged to transplant with ECMO. Of these, 16 died without transplant, five improved and were de-listed and 25 underwent transplantation, with 21 of these surviving to hospital discharge. The median ECMO duration was 6.7 days in the study.

Ventricular assist devices (VADs) are better suited to long-term support but are associated with the risks of bleeding, stroke and device-related infection. A recent multi-institutional review reports successful bridging to transplantation with VADs in 86% of children.

Rejection

Rejection remains a key factor limiting the lifespan of the transplanted heart. Rejection may be:

- hyperacute rejection, which is mediated by preformed antibodies and occurs in minutes to hours post-transplant;
- acute cellular rejection, which is mediated by T cells and occurs most commonly in the first six months following transplant;
- acute humoral rejection, which is mediated by antibodies and occurs in the first few weeks following transplant; and
- chronic (coronary allograft vasculopathy), which is both humoral and cellular, manifesting as diffuse atherosclerosis with myointimal proliferation in the coronary arteries, and occurs months to years following transplant.

Acute cellular rejection is classified according to the grading system of the ISHLT and requires endomyocardial biopsy. This can be performed using the transvenous approach, commonly via the right internal jugular or femoral veins. Endomyocardial biopsies are usually performed most frequently in the first three months after transplantation when the risk of cellular rejection is highest, and less frequently during the remainder of the first post-transplant year. Biopsies are performed in accordance with protocols, but a high level of suspicion should be maintained regarding the possibility of acute rejection episodes, as symptoms may be non-specific, such as fever, fatigue or increasing shortness of breath. Due to denervation of the transplanted heart, most patients will not be aware of chest pain in the presence of coronary artery disease or may have non-specific symptoms, and serial coronary angiography is usually employed as surveillance for chronic rejection (post-transplant coronary artery disease). Coronary allograft vasculopathy occurs in 25% of patients by seven years following transplantation.

Immunosuppression

Immunosuppression in children needs to take into account the maturation of the immune system and also that the pharmacokinetics of many immunosuppressive agents are affected by patient age. Immunosuppression aims to prevent rejection while avoiding the complications of immunosuppression (infection and malignancy) and the adverse effects of immunosuppressive agents (including organ toxicities). Specific immunosuppression regimes vary widely between centres but fall broadly into the following categories:

- induction therapy;
- maintenance therapy; and
- treatment of rejection episodes.

Induction Therapy

The aim of induction therapy is to avoid early acute rejection. ISHLT data indicate that induction therapy does not confer a survival advantage, but it may be indicated in selected patients, such as sensitised individuals or those with severe pre-existing renal dysfunction. Commonly used agents are polyclonal antibodies, such as antithymocyte globulin, which cause rapid T-cell depletion. Alternatives are monoclonal antibodies such as OKT3 (a murine antibody targeting the CD3 antigen on T cells) or Campath-1H (a humanised antibody directed against the CD52 antigen), which deplete T and B lymphocytes, NK cells and monocytes. Interleukin-2 receptor antagonists, basiliximab or daclizumab, may also be used. These are monoclonal antibodies that bind competitively to the CD25 antigen on activated T cells.

Maintenance Therapy

A wide variety of oral drug combinations are possible. Almost all children receive a calcineurin inhibitor, either cyclosporin or tacrolimus. Adequately powered studies have not been performed to examine survival between patients taking cyclosporine versus tacrolimus. Although ISHLT data suggest that there is no survival advantage for any particular agent, the use of tacrolimus is associated with a lower probability of requiring treatment for rejection in the first year after transplant. Cyclosporin causes hirsutism and gingival overgrowth, which may be unsightly and have an adverse impact on self-image. There is some evidence that hyperlipidaemia and hypertension occur less often with tacrolimus, although the frequency of post-transplant complications such as diabetes or post-transplant lymphoproliferative disorder may be higher.

Neonates who undergo transplantation can often be maintained on a single antirejection agent. Most children who undergo transplantation beyond infancy have the addition of an antiproliferative agent, either azathioprine or, increasingly, myophenolate mofetil (a more selective anti-lymphocyte therapy). The major adverse effects of azathioprine include leukopenia, anaemia and thrombocytopenia. The use of myophenolate mofetil is associated with lower mortality and less rejection in adults compared with...
azathioprine. However, its use may be associated with an increased opportunistic infection rate (mainly herpes simplex) compared with azathioprine use. Other troublesome adverse side effects include nausea, vomiting and diarrhoea.

Gluocorticoids are widely used in induction and maintenance regimes, as well as in the treatment of acute rejection episodes. They are potent immnosuppressive agents, in addition to having anti-inflammatory properties, but they have an important array of long-term adverse effects, which include cosmetic effects, hyperlipidaemia, diabetes, decreased bone density, growth retardation and adrenal insufficiency, all of which are of major concern in growing children. Approximately 50% of children can have their steroid therapy withdrawn after the first post-transplant year.

Target of rapamycin inhibitors, such as everolimus and sirolimus, are newer agents with both immnosuppressive and anti-proliferative properties. They have a potential role in the prevention of post-transplant coronary artery disease (chronic rejection) or in patients who have renal dysfunction secondary to calcineurin toxicity, but their long-term effects when used as primary therapy after transplantation have not yet been fully studied.

Treatment of Rejection Episodes

Acute cellular rejection may be treated with pulsed oral or intravenous steroids, antilymphocyte agents, an increase in current oral medication or a change to a different immnosuppressive agent. The treatment, or combination of treatments, chosen will depend on the severity of the rejection, the time elapsed since transplantation and the patient’s rejection history. Acute humoral rejection, which is much less common, may be treated with cyclophosphamide immunoglobulin or plasmapheresis, which are therapies aimed at removing the rejecting antibodies.

There is currently no reliable and universally successful treatment for established post-transplant coronary artery disease, which usually starts in the small coronary vessels and tends to be diffuse and progressive. Localised, discrete lesions can be dealt with using stents or coronary artery bypass. The routine use of pravastatin after heart transplantation has been shown to reduce the severity of post-transplant vasculopathy, lower the incidence of rejection and improve survival. Some of these benefits appear to be immune-mediated rather than the direct consequence of a reduction in lipids. Sirolimus may inhibit myointimal proliferation and may prevent short-term progression of coronary disease, but experience with this agent in children is still preliminary. At every clinic visit, attention should be paid to the patient’s compliance with his or her medication regime and to whether the child and responsible carer have a routine to ensure that medications are taken habitually.

Risk Factors for Mortality

Risk factors for one-year mortality are largely dependent on diagnosis and pre-transplant status. Patients with a congenital diagnosis have a relative risk of mortality at one year of 2.19; for those patients with a congenital diagnosis who require mechanical support, the relative risk is 4.16. There is also a significantly increased risk with pre-transplant ventilatory support, prostaglandin requirement, age less than one year and rejection requiring therapy during the first year. Re-transplantation for any reason also confers a significant increased risk (odds ratio 1.96). There is borderline increased risk with elevated panel reactive antibodies (greater than 10% gives an odds ratio of 1.31). Other variables that have a significant impact on mortality in the first year include donor age, creatinine, weight ratio, centre transplant volume and bilirubin.

The most common cause of death in long-term (more than 10 years) transplant survivors is coronary artery vasculopathy (accounting for 30–35% of deaths). Patients who undergo transplantation in infancy have a lower incidence of coronary artery vasculopathy than older recipients. Graft failure is the second leading cause of death (25%), followed by malignancies and infection. Deaths from acute rejection decline increasing with time from transplantation.

Quality of Life

Quality of life is good for most patients, with the majority of children being in NYHA functional Class I within a few months of transplantation. Formal exercise testing shows that peak exercise capacity is only about two-thirds that of normal subjects, primarily related to reduced peak heart rates in denervated transplanted hearts. Other factors, such as effects of immunosuppression and existing genetic, intellectual or physical disabilities, may also have an impact on quality of life.

Complications of Heart Transplantation

Complications of heart transplantation in children include:

- allograft rejection or dysfunction;
- immune complications of immunosuppression;
- non-immune adverse effects of immunosuppression; and
- psychological and social issues.

Allograft Rejection

Allograft rejection has been discussed previously. ISHLT data show that only 40% of paediatric patients are free from a rejection episode at one year post-transplant, the highest risk of first rejection episode...
occurring between one and two months after transplantation. The median number of treated rejection episodes per patient in the first year after transplantation is 1.8.

Rejection episodes that occur late (after the first year of transplantation) carry a relatively poor prognosis.22

**Immune Complications of Immunosuppression**

Infection is the second most common cause of death in the first year post-transplantation.4 After transplantation, children have an increased prevalence of the same infections seen in the general population, and these may cause increased disease severity. In particular, CMV and EBV, which are generally benign in the immunocompetent population, may cause problematic infections. These children are also at risk of opportunistic infections such as *Pneumocystis carinii*.23 The long-term prophylactic use of cotrimoxazole is directed towards minimising this complication.

EBV is strongly associated with development of post-transplant lymphoproliferative disorder (PTLD), which is the major neoplasm posing a threat to paediatric transplantation patients. PTLD may mimic the entire spectrum of lymphomas. The highest risk is to patients who are EBV negative at the time of transplantation and receive an EBV-positive donor or develop a primary EBV infection. Patients who have been exposed to EBV and are seropositive are also at risk.44 Between 5 and 15% of paediatric heart transplant patients develop PTLD25,26 and there is a substantial mortality risk, with probability of survival being 75% at one year and 67% at five years after diagnosis.27 Treatment usually entails lowered immunosuppression, discontinuation of an antimetabolite and the addition of antiviral agents such as acyclovir or ganciclovir. Chemotherapy may be required for those with monomorphic or persisting polymorphic lymphomas. Surgery or radiation is not usually necessary, but may also be required for obstructive or mass lesions, including tonsilar enlargement. Other malignancies are uncommon in children after heart transplantation.

**Non-immune Adverse Effects of Immunosuppression**

Common complications of currently used immunosuppressive agents are renal dysfunction, hypertension, hyperlipidaemia, decreased bone mineral density, bone marrow suppression and diabetes. Calcineurin inhibitors, in particular, may cause progressive renal dysfunction, and a change in immunosuppressive strategy should be considered if the serum creatinine is significantly elevated (usually more than twice the upper limit of normal). Routine post-transplant surveillance should include routine investigations to monitor for the known complications and adverse effects of therapy.

**Psychological and Social Issues**

Although most patients enjoy near-normal physical health following successful transplantation28 and are in age-appropriate school classes,29 many patients suffer problems with psychosocial adaptation30 and require ongoing support. Adolescents and young adults may cease compliance with their medication, and this can be a problematic time period, with increased rates of rejection and mortality. The transplant team should include both a social worker and a psychologist with experience in adolescent issues.

**Re-transplantation**

The survival half-life of paediatric transplant recipients is 12.5 years (ISHLT data). Therefore, many patients require re-transplantation while they are still relatively young. The most common indication for listing for re-transplantation is chronic allograft vasculopathy, and the survival rate following re-transplantation is acceptable but lower than that of patients undergoing primary transplantation. The waiting list mortality for retransplantation is relatively high, most likely due to the unpredictable consequences of diffuse coronary disease.31

**Future Directions**

A greater understanding of the host immune response to the transplanted organ will permit the development of more targeted drug regimes. These will allow advantage to be taken of drug synergism and allow a reduction in individual drug dosages, leading to fewer adverse effects and non-specific consequences of generalised immune suppression. The ‘holy grail’ of solid organ transplantation remains the induction of allograft tolerance so that long-term immunosuppression is not required and patients do not have the attendant risks of infection and malignancy. Young children with immature immune systems may be the most suitable candidates for these therapies.

**Summary**

Paediatric heart transplantation is an effective treatment for end-stage heart failure but requires surveillance for complications and long-term immunosuppressive therapy. Recent improvements in survival owe most to the reduction in early post-operative mortality. Future developments are likely to involve the newer immunosuppressive agents and the ability to modulate the immune response so as to minimise the need for long-term therapy.