Canadian Consensus on Paediatric and Adult Congenital Heart Transplantation 2004

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INTRODUCTION

The Need for Paediatric and Adult Congenital Guidelines

There is a large and rapidly growing literature that addresses heart transplantation for adult patients with anatomically normal hearts, with a much smaller literature concerning heart transplantation in children and in adult patients with congenital heart disease. Excellent consensus guidelines for adult patients have been published, but given the vast differences between adult patients and paediatric patients or adult congenital patients requiring heart transplantation, there is little reason to believe that these guidelines are applicable to these two latter populations.[1,2] One of the key issues that contributes to the differences between adult and paediatric transplantation is the wide range of ages that comprise the paediatric population and, hence the heterogeneity in size, stage of development and diagnoses. The other key factor, in contrast to the relative homogeneity in the adult population, is the wide range of diagnoses including anatomically normal hearts with functional compromise (with an extensive differential diagnosis and very unlikely to be ischemic in origin) to the broad spectrum of anatomical anomalies encompassed by the heading of "congenital heart disease" (CHD). Accordingly, in this document we have attempted to summarize the relevant literature and synthesize management guidelines for children and adult congenital patients requiring heart transplantation. The document that follows has been prepared in a consensus fashion, with input from paediatric

and adult congenital cardiologists and cardiovascular surgeons at all major medical sites involved in the care of these patients across Canada.

Cardiac transplantation is increasingly accepted as a treatment option for end stage heart disease (either functional, anatomic or both) in the paediatric and adult congenital population. Improvements in organ donation and preservation, surgical techniques, post-operative intensive care medicine, and anti-rejection therapy have resulted in improved survival rates following heart transplantation.[3,4] However, the challenges facing organ donation in Canada and worldwide as outlined in the adult consensus guidelines, are equally if not more apparent in the paediatric population.[1] Therefore, the availability of donor organs is a significant limiting factor to the wider application of heart transplantation to the paediatric and adult congenital population.

The purpose of this consensus document is to outline the indications and contraindications for heart transplantation in the paediatric and adult congenital population, to review the surgical management of the recipient and donor in the paediatric population, and to review post-transplant management including rejection, infection, transplant coronary artery disease (TCAD), malignancy and other complications pertinent to the paediatric population. Similar issues pertinent to the adult population are thoroughly covered in the adult consensus guidelines which will be referenced within this document as appropriate.[1]

Each recommendation in this document is ranked with regard to the level of supporting evidence:

- Level A recommendations are based upon multiple randomized clinical trials.
- Level B are based upon a single randomized trial or multiple non-randomized trials.
- Level C are based primarily upon expert consensus opinion.

The level of evidence upon which a recommendation is based differs from the strength of the recommendation. A given recommendation may be based upon randomized trials yet still be controversial. Other forms of therapy, which are based solely upon expert consensus, may be strongly recommended. Recommendations in this document adhere to the format of guidelines previously published by the American College of Cardiology (ACC) and American Heart Association (AHA).

- Class I: Conditions for which there is general agreement that a given therapy is useful and effective.
- Class II: Conditions for which there is conflicting evidence or a divergence of opinion concerning the usefulness and effectiveness of a therapy.
    - Class IIa: Weight of evidence/opinion favors usefulness/effectiveness.
    - Class IIb: Weight of evidence/opinion is less in favor of usefulness/effectiveness.
- Class III: Conditions for which there is general agreement that a therapy is not useful and (in some cases) may be harmful.

It is difficult to derive true population-based data on heart transplantation. Many factors may impact whether a patient is referred and listed for heart transplantation including a wide variability in decision-making around clinical need for transplantation, availability of expertise, individual center referral patterns, and medical team and familial belief systems. Therefore, the starting point for looking at natural history and outcomes is either at the point of listing for heart transplantation or once a patient undergoes a heart transplant. There are two main sources for data on outcomes related to paediatric heart transplantation: the Registry of the International Society of Heart and Lung Transplantation (ISHLT)[3] and the Pediatric Heart Transplant Study

(PHTS, a research database owned and operated by the Pediatric Heart Transplant Study Group).[4]

According to both ISHLT and PHTS, the annual number of paediatric heart transplant procedures has remained stable since the mid-1990s with approximately 350 worldwide annually, as has the age distribution.[3,4] In infants less than 1 year of age, CHD has remained the most common underlying diagnosis leading to heart transplantation. Cardiomyopathy remains the main diagnosis in the 1-10 year age group, though CHD has been increasing over the last few years. Cardiomyopathy continues to be the majority diagnosis in adolescents.

Currently, the expected overall one year survival after paediatric heart transplantation is 84%.[3,4] However, further supporting the marked differences even within the paediatric population, the conditional 4 year survival in the most recent era analyzed (1998-2002) for those who survive the first year is >90% for infant and childhood transplant patients and 85% for adolescents. There is a relatively constant 2% mortality per year after the first year following transplantation for infants and >3% for adolescents. Graft half-life was 17.5 years for age 1-10 years and 13.7 years for the adolescent age group. Graft half-life was not computable for the infant group with a 15 year survival of approximately 70%.[3]

INDICATIONS AND CONTRAINDICATIONS

Indications – General Considerations

Guidelines for listing adult patients for heart transplantation, based on a comparatively uniform population with a predictable natural history, have been published by both the American Society of Transplantation[2] and the Canadian Cardiovascular Society[1]. No such guidelines exist

for the paediatric population or for adults with complex congenital heart disease, though there are attempts in the literature to outline the relevant factors that should lead to consideration of listing for heart transplantation.[5-9] As in the adult population, criteria need to be designed to identify patients who are at the greatest risk of dying and/or who will derive the greatest benefit from cardiac transplantation. Standard guidelines applicable to the population as a whole are not feasible or practical given the heterogeneity of the ages and diagnoses. Guidelines for individual congenital heart lesions are discussed throughout the document.

In general, indications for paediatric heart transplantation can be divided broadly into two groups: life-saving or life-enhancing. Clearly, the edges separating these two "groups" are blurred and they may overlap in the same patient. In general, life-saving indications include the following:

End stage myocardial failure in the context of:

Cardiomyopathies or myocarditis

Congenital heart disease

Post-cardiotomy heart failure

Malignant arrhythmias refractory to medical or device management

Complex congenital heart disease with no options for surgical palliation at an acceptable risk

Unresectable cardiac tumours causing obstruction or ventricular dysfunction (systolic or diastolic)

Unresectable ventricular diverticula

Life-enhancing indications include treatment of excessive disability, unacceptably poor quality of life, or long-term morbidity in the setting of failing myocardial function, complex congenital heart disease, profound cyanosis, or after failed surgical palliation of congenital heart disease.

Contraindications – General Considerations

Part of the purpose of a **pre-transplant assessment** should be to identify factors that are potential contraindications, and to decide whether they are compelling enough to preclude candidacy for organ transplantation. Most routine pre-transplant assessments, from a non-cardiac point-of-view, include a thorough history and physical examination, screening laboratory investigations reflecting hematologic, hepatic, and renal function, baseline infectious diseases, and panel reactive antibodies (PRAs, see below). Further investigations, diagnostic imaging and/or consultations should be individualized by patient (i.e. neurologic and/or genetic-metabolic testing, etc.).

Cardiopulmonary contraindications to heart transplantation in the paediatric population include fixed pulmonary hypertension, pulmonary vein atresia or progressive stenosis, and severe uncorrectable hypoplasia of the branch pulmonary arteries or the thoracic aorta. Other contraindications, which can be relative, include irreversible multisystem organ failure, progressive systemic disease with early mortality, morbid obesity, diabetes mellitus with end-organ damage, hypercoagulable states, and *severe* chromosomal, neurologic, or syndromic abnormalities. Patients should be assessed on an individual basis if the major contraindication is active infection, especially if it is being appropriately treated with good clinical response. In a recent review of risk factors for transplantation at the Hospital for Sick Children in Toronto, significant fungal infection was a risk factor for poor outcome, but bacterial infection did not

play a role in survival to hospital discharge.[10] Likewise with malignancies, patients should be assessed on an individual basis based on the type of malignancy as there are reports of successful heart transplantation in a number of paediatric malignancies in remission (especially for anthracycline-induced cardiomyopathies).[11-13] Complicating factors that are no longer considered contraindications to heart transplantation include complex congenital heart disease (abnormalities of situs, systemic venous abnormalities, anomalous pulmonary venous drainage without stenosis, some pulmonary artery anomalies), previous sternotomy/thoracotomy, non-fixed pulmonary hypertension, non-cardiac congenital abnormalities, kyphoscoliosis with restrictive pulmonary disease, nonprogressive or slowly progressive systemic diseases with life expectancies into the 3rd or 4th decade (genetic or metabolic cardiomyopathies), and diabetes mellitus without end-organ damage.

Functional Class

As outlined in the adult consensus guidelines[1], it is well accepted that advanced symptoms of heart failure (HF) are associated with a worse outcome, especially in patients with recent or recurring hospitalizations. The New York Heart Association (NYHA) classification is widely used for grading HF in adult patients because of its simplicity in providing a practical assessment of functional limitation. It is an ordinal scale defined by the degree to which symptoms of HF limit a patient's physical activity. However, the applicability to the paediatric population is limited.

Several scoring systems have been proposed for grading HF in children. The most widely used is the Ross Classification (Table 1).[14] In 1994 the Ross Classification was adopted by the Canadian Cardiovascular Society as their official system for grading HF in children,[15] and

the system is currently used in the national Cardiomyopathy Registry and in a multicenter study of carvedilol.

Table 1: Ross Classification

Class	Interpretation
I	Asymptomatic
II	Mild tachypnea or diaphoresis with feeding in infants. Dyspnea on exertion in older children.
III	Marked tachypnea or diaphoresis with feeding in infants. Prolonged feeding times with growth failure due to HF. In older children, marked dyspnea on exertion.
IV	Symptoms such as tachypnea, retractions, grunting or diaphoresis at rest.

Another system has a 12-point scale based on quantity and duration of feeding, respiratory rate and pattern, heart rate, peripheral perfusion, presence of a diastolic filling sound, and degree of hepatomegaly.[16] Finally, there is the New York University Pediatric Heart Failure Index in which a total score from 0 – 30 is obtained by adding together points based on physiologic indicators and the patient's specific medical regimen.[17] Neither of these systems have been validated in large numbers of children nor tested against biological markers of HF or exercise capabilities.[18]

Overt HF symptoms occur late in the disease process, indicating a failure of compensatory mechanisms. Functional class can be affected by adjustments in medical management and should not be the sole requirement for listing. Both the NYHA and Ross HF scales concentrate on current symptoms and do not discriminate well between early vs. chronic or stable vs. decompensated HF. The ACC/AHA 2002 HF guidelines therefore advocate a HF classification schema that identifies patients at risk for HF who require early intervention to prolong the symptom-free state, and it also delineates patients who require aggressive management of symptoms once they become manifest that can also be applied to the paediatric population.[19,20]

Table 2: Proposed Heart Failure Staging for Infants and Children

Stage	Interpretation
A	Patients with increased risk of developing HF, but who have normal cardiac function and no evidence of cardiac chamber volume overload. Examples: previous exposure to cardiotoxic agents, family history of heritable cardiomyopathy, univentricular heart, congenitally corrected transposition of the great arteries.
B	Patients with abnormal cardiac morphology or cardiac function, with no symptoms of HF, past or present. Examples: aortic insufficiency with LV enlargement, history of anthracycline exposure with decreased LV systolic function.
C	Patients with underlying structural or functional heart disease, and past or current symptoms of HF.
D	Patients with end-stage HF requiring continuous infusion of inotropic agents, mechanical circulatory support, cardiac transplantation or hospice care.

Cardiopulmonary Testing

Functional testing provides an objective assessment of the degree of limitation that can be followed in a serial manner, is correlated with survival, and allows consistency across transplant programs if patients are old and cooperative enough for exercise testing.

Anatomically normal heart

In the adult literature, although some controversy exists over the degree of impairment in exercise required to justify transplantation, in general, patients with peak oxygen consumption (VO_2) less than 10 ml/kg/min should be listed for Tx.[2] Patients with a VO_2 > 18 ml/kg/min will experience one-year survival rates above 95% and should be followed expectantly.[2] Management of patients with a VO_2 between 10 and 18 ml/kg/min remains controversial. A blunted systolic BP response to exercise (systolic BP at peak exercise <120 mmHg), and/or chronotropic incompetence, when associated with a VO_2 <15 ml/kg/min or a peak VO_2 <50% predicted help redefine the prognostic value of intermediate VO_2 values.[2,21] There are no

objective numbers for the abovementioned parameters that are generally accepted in the paediatric population, and percent predicted values have to be taken into consideration.

Congenital heart disease

The situation in patients with CHD is much more complicated. Baseline "normal" VO_2 values for patients with different types of palliated CHD are not fully delineated, especially if one also considers age, size and sex. This may be further affected by the presence or absence of residual lesions, chronic cyanosis, and heart failure. Therefore, the role of cardiopulmonary testing at present is to compare serial tests in the same patient over time for objective evidence of clinical deterioration in functional status.

Pulmonary Hypertension

Pulmonary hypertension is an important and frequent accompaniment of CHD and/or heart failure. The preoperative status of the pulmonary vascular bed, especially the resistance vessels, is a major determinant of the presence and degree of residual postoperative pulmonary vascular disease. Pulmonary hypertension is fixed or irreversible if there is no response to pharmacologic manoeuvres. Reactive pulmonary hypertension implies that functional pulmonary arteriolar constriction attributed to dysfunctional vascular smooth muscle tone contributes to the elevated pulmonary pressure and is likely to reverse with vasodilators. Reactive pulmonary hypertension may precede irreversible pulmonary arteriolar disease.[22]

A full discussion of the assessment of pulmonary hypertension is beyond the scope of this document. However, when assessing a patient for heart transplantation, the presence and reversibility of pulmonary hypertension must be aggressively evaluated during a right heart catheterization.[5,22,23] Patients with a reactive component of pulmonary hypertension can be

identified through different manoeuvres. Inhaled oxygen at 100% with repeated measurements is used in the congenital population, especially when cyanosis is present.[24] Intravenous vasodilators such as tolazoline, nitroprusside, prostaglandin E1, prostacyclin, milrinone or adenosine can be tested.[22,23,25] Inhaled nitric oxide is a potent, rapidly acting vasodilator that is a valuable tool in the preoperative evaluation of patients with heart disease and pulmonary hypertension.[26,27]

Preoperative pulmonary vascular resistance (PVR) is an independent risk factor for early and late death after heart transplantation.[28] Right ventricular dysfunction accounts for approximately 50% of cardiac complications and 20% of early deaths post-transplant.[29,30] The actual degree of pulmonary hypertension precluding heart transplantation is varied as there is a continuum of increasing risk as PVR rises. The consensus in the adult population is that a pulmonary artery pressure greater that 50 mmHg systolic, PVR greater than 4 Wood units, PVR index greater than 6 Wood units or transpulmonary gradient greater than 15, measured after aggressive challenge should be contraindications to heart transplantation.

Likewise, in the paediatric population, elevated pulmonary vascular resistance (PVR) is an independent risk factor for mortality both early and late after heart transplantation.[6,31,32] Gajarski, et al, reported intermediate outcomes in 8 paediatric patients with PVR greater than 6 units$\bullet m^2$.[32] He concluded that it is the reactivity of the vascular bed as opposed to the absolute measure of PVR that correlated with outcome.

An added consideration in the paediatric population with congenital heart disease is the presence of "obligatory" pulmonary hypertension. Infants with single ventricle physiology (i.e. hypoplastic left heart syndrome), have obligatory systemic pulmonary pressures. All newborn infants have elevated pulmonary pressures and pulmonary vascular resistance which would

normally require 3-6 months for complete vascular remodelling and normalization. Patients with restrictive cardiomyopathy of any age may have elevated pulmonary pressures and demonstration of reversibility may not be straightforward given the underlying pathophysiologic mechanism. Therefore, depending on the diagnosis and age of the patient, specific assessment of pulmonary hypertension may not be clinically warranted prior to heart transplantation. When correctly assessed and interpreted, the issue of elevated pulmonary resistance in patients with congenital heart disease is not a contraindication to cardiac transplantation.[31]

Eisenmenger's syndrome with an uncorrected intracardiac defect or uncorrectable congenital heart disease with atresia or diffuse severe hypoplasia of the pulmonary arteries and progressive heart failure are indications for heart-lung transplantation.[6,22,31,32] Lung transplantation with repair of the cardiac defect when feasible, is another option that can be effective in reducing pulmonary hypertension. It is well recognized that single lung transplant for pulmonary hypertension may have a potentially difficult post-operative course.[33] Forty percent of heart-lung adolescent recipients had a diagnosis of congenital heart disease.[34]

Neonatal Advantage

There is accumulating evidence that there may be an advantage to transplanting patients in early infancy.[3,35] As outlined above, there is consistent evidence from survival curves that infants less than 6 months of age have an improved long term survival (out as far as 15 years) compared with older age groups. The 4 year conditional survival for infants transplanted at less than one year of age who survive to one year post-transplant is now greater than 90%.[4] At Loma Linda University, which has the largest infant transplant population worldwide and is now following 184 survivors of infant transplantation ranging in age up to 17 years, transplantation

during the first month of life appears to offer a distinct advantage compared to transplantation even during the remainder of the first year of life, with 80% overall survival at 5 years. For 97 infants transplanted during the first month of life, actuarial survival at 13 years is now 77%.[36] This advantage is believed to be due to the relatively mild immunologic response of the newborn recipient, with only rare deaths or re-transplantation due to rejection, and heightened sensitivity of the infant to immunosuppressive therapy. Late episodes of acute cellular rejection are rare in infant transplant recipients. The risk of death from TCAD remains a much less significant problem than in adult transplant patients (<2% risk of death over the first 5 years), which is likely an important factor contributing to the low incidence of late deaths in the infant transplant group. This survival advantage should be taken into consideration when considering options for infants with complex CHD (i.e. high risk surgical palliation versus cardiac transplantation).

ABO-Incompatible (ABO-I) Transplantation

Despite the very promising results offered by infant heart transplantation, the number of organ donors of suitable size for infant recipients is limited, thus preventing effective expansion of this therapy to all patients in need. In statistical work from PHTSG using competing outcomes analyses[36-38], studies of transplant listing outcomes for infants less than 6 months of age showed that by 6 months after listing, most patients had either been transplanted (61%) or had died waiting (27%). One of the factors increasing the risk for death while waiting included recipient blood type O, due to allocation of some organs from group O donors to recipients of other blood groups. Thus, there is compelling need for strategies to expand the donor pool for infants.

Heart transplantation between donors and recipients with incompatible blood groups is usually contraindicated because of the high risk of hyperacute rejection. Newborn infants do not

produce isohemagglutinins and the complement system is not fully developed. West, et al., have clearly demonstrated that heart transplantation across major blood groups is safe in the infant population and postulate that this may reflect the immaturity of the infant immune system or even represent the first human example of neonatal transplantation tolerance.[39] The obvious advantage of ABO-I transplantation is a reduction in waiting time and waiting list mortality. Immunologic advantages have been proven (i.e. tolerance or graft accommodation).[40] A detailed description of the protocol for performing ABO-I heart transplantation in the infant population can be found in the reference.[39] Particular attention must be given to the blood products used at the time of the surgery on pump and those administered afterwards. Any antibodies to donor blood group surface antigens must be removed prior to removal of the aortic cross clamp and reperfusion of the heart. In general, these patients follow the same post-operative immunosuppression management and rejection surveillance protocol as the ABO-compatible infant patient population with the exception of routine surveillance for production of isohemmaglutinins (anti-A and anti-B antibodies).

1. Recommendations: Indications and Contraindications (Level C)

Indications

A. End stage myocardial failure despite maximal medical therapy
B. Malignant arrhythmias refractory to medical, surgical or device management
C. Complex congenital heart disease with no options for surgical palliation at an acceptable risk
D. Unresectable cardiac tumours causing obstruction or ventricular dysfunction (systolic or diastolic)
E. Unresectable ventricular diverticula

F. Progressive cyanosis in the presence of complex CHD that is not amenable to surgical repair or palliation or for which surgery is associated with unacceptable mortality

G. Excessive disability, unacceptably poor quality of life, or long-term morbidity in the setting of failing myocardial function, complex congenital heart disease, or after failed surgical palliation of congenital heart disease.

H. Advanced functional class and/or heart failure stage (Class III, IV or Stage D – See Tables 1 and 2)

I. Low or deteriorating peak $V0_2$ predicted for diagnosis, age, sex and body size.

J. Presence of progressive pulmonary hypertension that would preclude heart transplantation at a later date.

K. Absence of contraindications

L. Potential to undergo rehabilitation after transplantation

Note: Neonates and infants requiring heart transplantation should be offered ABO-incompatible organs given the decreased waiting list mortality and the survival advantage of infant transplantation

Contraindications – Absolute and Relative

A. Anatomic: pulmonary vein atresia or progressive stenosis, severe uncorrectable hypoplasia of the branch pulmonary arteries, severe hypoplasia of the thoracic aorta

B. Pulmonary hypertension: relative contraindication based on patient age, underlying disease/heart defect, degree of pulmonary hypertension, and response to aggressive testing in cardiac catheterization laboratory for evidence of reactivity if warranted.

C. Irreversible multisystem organ failure

D. Progressive systemic disease with early mortality (genetic/metabolic, idiopathic, syndromic)

E. Morbid obesity

F. Diabetes mellitus with evidence of end-organ damage

G. Severe chromosomal, neurologic or syndromic abnormalities

H. Active infection: patients should be assessed on an individual basis (see text)

I. Malignancy: patients should be assessed on an individual basis (see text)

Anatomically Normal Heart in the Paediatric Population

In general, patients with an anatomically normal heart and HF have some form of cardiomyopathy, the majority of which are idiopathic. The spectrum of etiologies for HF in children is considerable, and a discussion of the diagnostic approach to children with HF is beyond the scope of this manuscript, but is well covered elsewhere in the literature.[41-43] A thorough work up for etiology should be undertaken as certain genetic or metabolic conditions may be either amenable to treatment or, more likely, affect prognosis and eligibility for heart transplantation. Paediatric patients with a syndrome of HF should be managed as per current state of the art recommendations for the management of HF, for which there have been recent excellent consensus guidelines developed.[20] Transplantation should be considered when patients are deteriorating despite optimal medical and supportive management. Functional class and HF stage should be assessed initially and in response to medical therapy as outlined above (See Functional Class).

Patients with restrictive cardiomyopathy and chronic diastolic dysfunction are at high risk for sudden death, as well as for developing secondary pulmonary hypertension, which limits survival, and should be evaluated for heart transplantation, especially when not responsive to optimal medical management (HF Stage C, Table 2).[44-47]

Congenital Heart Disease in the Paediatric Population

Univentricular circulation

For most patients with single ventricle anatomy, surgical management is the primary treatment. This includes a variety of early palliative procedures followed by bidirectional cavopulmonary connection (BDCPC, Glenn), and ultimately the Fontan procedure (total cavopulmonary connection, TCPC). The complete and obligatory mixing of systemic and pulmonary venous flow in the early palliation requires that ventricular output be maintained at a level that is 2 to 3 times normal.[48,49] This chronic volume overload places the myocardium at considerable risk.[48] There is ongoing debate as to the importance of the systemic ventricular morphology on the outcome before and after Fontan, with differing reports on the size, function, and long term outcome of a morphologically single left vs. single right ventricle.[50-55]

Rarely infants, who have completed the first stage of palliation, present with symptomatology related to heart failure with or without myocardial dysfunction including tachypnea, tachycardia, hepatic congestion, cyanosis, and failure to thrive. Patients should be assessed for anatomic lesions contributing to the symptomatology (obstructions to pulmonary or systemic blood flow, valvular regurgitation, etc.), and/or rhythm disturbances, and/or myocardial dysfunction and managed accordingly – either medically or by catheter or surgical intervention. Patients with identified problems that preclude progressing to the next palliative stage should be assessed by functional class and HF stage (see Functional Class above), and referred for heart transplant assessment when appropriate.

In patients who have completed the bidirectional Glenn or Fontan palliation, the manifestations of HF may not include the typical symptoms that occur in patients with 2

ventricles, and can be related to factors other than myocardial dysfunction. These patients experience peripheral edema, pleural and pericardial effusions, cyanosis, and symptoms related to reduced cardiac output such as chronic fatigue, loss of appetite, and exercise intolerance. Patients should be assessed for anatomic lesions contributing to the symptomatology (obstructions within the venous circuit, outflow tract obstruction, valvular regurgitation, etc.), and/or rhythm disturbances, and/or myocardial dysfunction and managed accordingly – either medically or by catheter or surgical intervention. Failing this and with persistent symptomatology, patients should be assessed by functional class and HF stage (see Functional Class above), and referred for heart transplant assessment when appropriate.

Exercise performance in children with successful or optimal Fontan palliation may be quantitatively identical to that in children with mild HF – highlighting the importance of not making judgments based on peak VO2 alone in the palliated patient with CHD. Multiple factors contribute to this including diminished stroke volume, chronotropic incompetence, and exercise-induced hypoxia.[56-63] Therefore, whenever feasible, objective functional assessment of failing Fontan patients should be done serially in order to document individual deterioration in peak VO2 as opposed to making decisions based on an absolute value (see Cardiopulmonary Testing above).

Rarely, infants with complex congenital heart disease may present with lesions in which the risk of staged surgical palliation is very high (i.e. complex univentricular circulation with significant atrioventricular valve regurgitation or decreased myocardial function). In these cases, primary heart transplantation is an option, the major limitation being the ability to support the patient pending availability of a donor organ.

Primary heart transplantation for what is considered to be anatomy with a low risk for staged surgical palliation remains controversial and is centre-dependent. Advantages include higher post-transplant survival due to neonatal advantage (see Neonatal Advantage above). Disadvantages include donor organ availability and the ability to support the infant medically without complications prior to transplantation.

Other forms of CHD in the paediatric population

The majority of diagnoses of CHD in the paediatric population are amenable to either corrective or palliative surgery with increasingly good outcomes. However, sometimes a surgical approach fails – either acutely in the form of post-cardiopulmonary bypass myocardial failure, or chronically due to multifactorial reasons (anatomy, rhythm disturbances, etc.). In both of these situations, heart transplantation may become a consideration when all medical, interventional and surgical options have been utilized, and based on functional class and HF stage. The disadvantages of initial surgical palliation from a transplant point-of-view include potential sensitization of the patient (see Sensitized Patients below) and potential loss of the neonatal advantage (see Neonatal Advantage above).

Adult Congenital Heart Disease

The admirable progress made in cardiac surgery, technology and intensive care over the past 40 years have enabled 85% of the babies born with CHD to reach adolescence and adulthood.[64] As a result, the number of adults with CHD is growing rapidly and the attention is focused on long term survival. Most patients who underwent corrective repair in infancy remain vulnerable to late complications. With time, conduits become stenotic, valvular lesions progress, arrhythmias are more frequent and ventricular failure occurs. Complications vary according to

the native anatomy or type of surgical repair. Unoperated, palliated or repaired patients with or without pulmonary hypertension (mainly those with atresia, single ventricle physiology, transposition variants and pulmonary hypertension) may come to consideration for heart transplantation.

Congenital heart disease represents 3% of all heart transplantation in adults.[65] Criteria and timing for transplantation in this heterogenous group of patients are difficult to develop. Prognostic indices of outcome and pre-transplant survival such as functional class and VO_2 max have not been identified for the paediatric population, much less for adults with congenital heart disease (CHD).

Series on heart or heart-lung transplant in adults with CHD are limited to a total of 93 patients.[5,6] In addition to these data, important information can be extracted from larger series which include adults with CHD.[7,65] The majority of patients are in their 3rd or 4th decade.[5,6] The most common diagnoses prior to heart transplant are pulmonary and tricuspid atresia (with or without the Fontan operation) and transposition complexes.[5,6] Despite the numerous challenges posed by this group of patients (see Surgical Techniques below), survival after heart transplant for adults with CHD is similar to institution-matched patients without CHD in corresponding eras.[6,7,65] Reported actuarial survival at 5 years for adults with CHD receiving a heart transplant between 1985 and l999 varies from 60%[6] to 86%[7] depending on the institution.

Transposition of the great arteries – status post-atrial switch procedure

Children who have undergone atrial switch procedure (Mustard or Senning) at an early age do not have a normal life expectancy. Excellent long-term survival has been reported with most patients remaining asymptomatic until their thirties but, in a large single center retrospective study of 534 children who underwent the Mustard operation, Gelatt and al. reported

a 5-year survival of 89% and a 20-year survival of 76%.[66] Ventricular failure and arrhythmias were the most common modes of death after this operation. The major concern for these patients is the capability of the systemic morphologic right ventricle (RV) to work against an increased afterload over a long period of time without failing.

The long-term course is generally marked by right ventricular hypertrophy and dilation with progressive decrease in systolic function combined with progressive tricuspid regurgitation. Frequently, the degree of ventricular dysfunction is quite advanced by the time of clinical symptoms. Unfortunately, no medication has yet been proven effective in preventing RV dysfunction. The incidence is difficult to evaluate as most series report on selected populations with different lengths of follow-up.[67,68] Assessment of RV function is extremely challenging because of the particular shape of this ventricle that does not lend to any geometric model. No single simple method presently exists for RV evaluation and echocardiography, radionuclide ventriculography, magnetic resonance imaging or angiography are all complementary diagnostic tools. .

Discordance exists between the reduced RV systolic function and the reported asymptomatic state of many patients late after this operation. Looking at exercise capacity, in patients late after a Mustard procedure (10 to 20 years after), most series report lower mean maximal systolic blood pressure, heart rate, oxygen consumption and treadmill times compared to normal subjects.[69-71] Asymptomatic and mildly symptomatic Mustard patients (NYHA I-II) can have a maximum oxygen consumption as low as 20.0 ± 6.3 ml/kg^{-1}/min^{-1}.[71] There is no known relationship between the maximum oxygen consumption level, the patient's symptoms, the right ventricular ejection fraction or the prognosis. Therefore, the role of cardiopulmonary

testing at present is to compare serial tests in the same patient over time for objective evidence of clinical deterioration in functional status.

Surgical therapies for progressive RV failure, including tricuspid valve replacement and left ventricular reconditioning followed by anatomical correction (arterial switch) have had variable success in adult patients.[72] Evaluation for heart transplantation is indicated in symptomatic patients (NYHA III-IV) with severe RV dysfunction despite optimal medical therapy. Pre-transplantation assessment should include RV evaluation with echocardiography, radionuclide angiography and if possible, magnetic resonance imaging. Cardiac catheterization should be performed in order to eliminate baffle obstruction, and to measure right and left ventricular pressures and pulmonary vascular resistance. Patients should probably be listed if they are symptomatic despite medical therapy (NYHA III-IV), if the evaluation confirms severe ventricular dysfunction, if the maximal oxygen consumption is below 20 $ml/kg^{-1}/min^{-1}$ and is deteriorating, and before a significant increase in pulmonary vascular resistance is seen. It is possible, if needed, to support the systemic morphologic right ventricle with a left ventricular assist device to bridge these patients to transplantation.[73]

Pulmonary atresia with ventricular septal defect (PA-VSD)

PA-VSD is a heterogeneous form of CHD which has been subdivided based on the anatomy of the pulmonary circulation and the source of pulmonary blood flow (PBF), both of which are the most significant determinants of outcome.[74] Sources of PBF include native pulmonary arteries, major aortopulmonary collateral arteries (MAPCA's), or both.

Unoperated patient survival is dependent on the adequacy of pulmonary blood flow and exhibits a bimodal mortality pattern. The majority of unoperated patients with inadequate aortic-to-pulmonary blood flow die in infancy or childhood. A small percentage survive to

adulthood because of adequate but not excessive aortic-to-pulmonary circulation, but one-third of all unoperated adult survivors die at a mean age of 31 years.[75] Staged reconstructive operations, including complete or near-complete separation of the pulmonary and systemic circulations with unifocalization of PBF, are now performed and survival into adulthood is well-documented.[75,76]

There are limited data on adults with PA-VSD with only a single institution series focusing on 38 patients who were either unoperated, palliated or repaired at or beyond the age 18yrs.[75] In this series, all unoperated patients were equally divided between NYHA Class II and III, most palliated patients were in NYHA class II and most patients who underwent physiologic repair as adults were in NYHA class I. The mean oxygen saturation was 85% in unoperated and palliated patients with less than 20% of patients having symptoms of hyperviscocity secondary to erythrocytosis. Moderate or severe aortic insufficiency was more common in unoperated patients. Approximately one third of unoperated or palliated patients had decompensated right, left or biventricular heart failure.

Consideration should be given to transplantation when significant incapacity occurs on account of severe hypoxemia and/or congestive heart failure. For the presenting acyanotic adult who has undergone previous unifocalization, consideration should be given to transplantation for indications applicable to other adults with CHD as outlined in the first recommendation. Because of the extent of the cardiac disease in addition to the abnormal arborization of the pulmonary vascular bed typically in both lungs, heart-lung transplant is likely to be the most feasible option.[77] Heart transplant alone is usually contraindicated because of the extensive anatomic and physiologic PBF abnormalities. Single or double lung transplant with intracardiac repair may be possible in highly experienced centers.[78] Lung transplant with intracardiac repair is contraindicated when left heart disease occurs and right ventricular dysfunction is irreversible. Although there are no specific

contraindications to combined heart-lung transplant, there is added complexity in this group of patients. For such patients, the need for referral to centers where experience exists not only in heart transplantation, but also lung transplantation and adult congenital heart disease cannot be over-emphasized.

Specific pre-transplant investigations in this group of patients are undertaken to document: cardio-pulmonary anatomy; complications related to previous interventional procedures; physiology related to erythrocytosis if the patient is cyanotic; the presence or absence or pulmonary hypertension; right ventricular function and functional capacity. Proximal and distal pulmonary artery anatomy as well as the site and number of collaterals need to be determined. Pulmonary vascular reactivity studies may be required to document the presence or absence of pulmonary hypertension. Cyanotic patients need to be investigated for bleeding diathesis as well as other systemic complications well documented in the presence of chronic cyanosis.[79]

Fontan

As indicated above, the Fontan procedure is the final stage of a palliative surgical approach to most forms of univentricular circulation. The late results in the Fontan and the modified Fontan procedures depend on a number of factors including ventricular function. The reported average 10-years survival following Fontan operation is approximately 60%, rising to 80% in ideal situations.[80,81] Five years after Fontan operation, 80% of the patients are in NYHA class I or II. After 10 years, 75% are still in class I or II.[82-84] Similar to that observed in the paediatric age group, in the adult Fontan patients, the peak VO2 is diminished as compared to the normal population, some achieving only 35% of the normal reference values.

Obstruction to pulmonary blood flow and atrial thrombus formation often associated with atrial fibrillation are among the most serious immediate and long-term haemodynamic sequelae

following Fontan-type procedures.[81] In patients who were operated at an older age, the longstanding left ventricular volume overload may result in valve annulus dilation with resultant atrioventricular valve regurgitation and deterioration of left ventricular function (systolic and diastolic).[82,83] Other significant problems include protein-losing enteropathy (PLE), recurrent or refractory atrial dysrrhythmias, thromboembolism (systemic and pulmonary) and increasing cyanosis because of systemic venous collateralisation. In patients with a systemic right ventricle, the frequency of heart failure is very high. The presence of symptoms is associated with worse ventricular dysfunction, atrial tachyarrhythmias, fatigue and lower functional capacity. The mortality rate in these symptomatic heart failure patients is very high (>30%) as compared to asymptomatic patients (0%). Patients with a failing Fontan circulation should be evaluated and managed as noted above (see CHD in the Paediatric Population – Univentricular Circulation).

Most patients are referred for transplantation because of progressive heart failure, intractable PLE, and/or pulmonary arteriovenous malformations with progressive cyanosis. When PLE develops (up to 10% of patients) and obstruction of the Fontan has been excluded, the five-year survival is approximately 50%.[85] There is little experience with PLE after transplantation. However, in one small retrospective study, there were cases of continuous or recurrent protein loss as well as patients that were completely cured post-transplantation.[86]

Cardiac decompensation and the need for inotropic support is a sign of imminent death. Bernstein and colleagues found that among post-Fontan patients who are dependant on intravenous inotropes at the time of listing for transplantation, over one third die before a heart transplant can be performed.[87]

Congenitally corrected transposition of the great arteries in the adult

Congenitally corrected transposition of the great arteries (also known as L-TGA, or CC-TGA) is a rare form of CHD. There is a high incidence (>60%) of coexistent defects, including pulmonary stenosis, tricuspid (systemic) valve deformities and regurgitation, ventricular and atrial septal defects, and complete heart block. In the absence of associated defects, patients may be asymptomatic for many years, until systemic RV failure develops. Survival into the sixth and seventh decades has been documented; in many cases with remarkably few symptoms. Estimated life expectancy at present is approximately the fourth to fifth decade. With associated defects, symptoms typically develop sooner and require palliative surgical intervention, including pacemaker insertion, systemic tricuspid valve replacement, pulmonary outflow tract replacement (usually with a conduit), septal defect closures and 'double switch' procedure (two stage operation where the left ventricle is 'trained' using pulmonary artery banding to increase LV afterload, followed some time later by atrial and arterial switch procedures). Operative mortality rates are variable and probably relate to both centre experience and patient selection.[6,9,88-90]

Patients with L-TGA tend to have few symptoms, most in NYHA I or II, despite reduced exercise capacity when measured objectively. Measured ejection fractions also tend to be reduced and this finding generally predates occurrence of symptoms for several years. Symptom progression may occur as early as the late teen years, or as late as the fourth or fifth decade. Heart failure usually develops due to progressive systemic tricuspid valve regurgitation in the setting of poor systemic RV systolic function, both of which can be associated with the development of pulmonary hypertension. Medical treatment of end stage HF in this group is difficult once NYHA III/IV CHF develops. Patients with L-TGA who develop NYHA IIIb/IV

despite optimal medical therapy, in association with severe tricuspid regurgitation (or prosthetic valve), and who are not candidates for further operative intervention should be considered for heart transplantation. To date, no clinical or investigative variable has been shown to predict very high 1 or 2 year mortality in this group other than severe, refractory symptoms of CHF.

MANAGEMENT OF THE RECIPIENT AND DONOR

Surgical Techniques

General Considerations

Certain technical considerations are particular to heart transplantation in patients with CHD. Additional operations are required in up to 75% of patients, the most common of which are the takedown of a Fontan or Glenn anastomosis and pulmonary artery reconstruction.[6] The average patient has had between 2 and 3 prior operations.[6] The occurrence of previous thoracotomies compounds the associated increased risk of bleeding with acute hemorrhage being the most common cause of early mortality[7] and infection including mediastinitis being the most common complication.[6] Entry to the chest may be more complicated, particularly if extracardiac conduits have been used and have adhered to the back of the sternum. Prior interventional procedures may challenge access for cardiopulmonary bypass. The bleeding diathesis conferred by chronic cyanosis is yet another risk factor.

Bicaval vs biatrial anastomosis

There are different surgical approaches for the surgical procedure in the recipient.[91] Several retrospective studies have looked for differences in outcomes related to the type of approach. The bicaval approach, which is currently the standard in the adult population, has

been described to be associated with fewer tachyarrhythmias, slightly better hemodynamics, less tricuspid regurgitation, less pacemakers and better exercise tolerance than a biatrial anastamosis.[92-94] Other studies have shown no differences[95], or only differences in the incidence of atrial tachyarrhythmias.[96] The only randomized trial demonstrated that the bicaval technique had better hemodynamics and survival.[97] The biatrial technique has been associated with conduction disturbances requiring pacemaker placement in 4-15%[98], a higher thromboembolism risk, poor atrial synchrony, and more atrioventricular valvular regurgitation due to distortion of atrial anatomy.[99]

The preponderance of retrospective data supports a potential benefit related to the bicaval approach in adult heart transplant recipients. The most consistent finding is improved atrial function followed by a reduction in tricuspid regurgitation. There is conflicting data about the requirement for pacemaker therapy and atrial arrhythmias, both short and long term after transplantation. However, in the paediatric population, patient size, heart location, situs, systemic venous, and pulmonary venous anatomy must all be taken into consideration when determining the surgical approach. Some surgeons have been reluctant to use the bicaval approach, especially in infants, because of the risk of venous stenoses, but much success has been met in the interventional cardiac catheterization laboratory both dilating and stenting narrowed venous connections, thus allowing for application of the bicaval technique to a younger patient population.

Cardiac position and situs

When the recipient heart is in the dextrocardia position (the apex is pointing rightward) there may be a lack of space in the left pericardium to accommodate the donor heart. This can be simply remedied by opening the left pericardium and forming a flap, thus allowing the heart to

sit in part in the left chest. A lower donor to recipient size ratio could be sought to possibly avoid irreversible atelectasis of the left lung.

The vena cava and right atrium are on the left side in situs inversus. In order to create right-sided superior and inferior vena cava orifices for the donor heart, one of two techniques has been used. An interatrial tunnel is formed using recipient atrial tissue and/or pericardium followed by a biatrial anastomosis. A second technique using synthetic grafts or homograft material extends the vena cava to the right for bicaval anastomosis. In the case of normally positioned great vessels or corrected transposition of the great arteries, the great vessels and left atria are normally situated thus easily connected. Both techniques make endomyocardial biopsy challenging and stenosis of the caval reconstruction has been described.

Systemic and pulmonary venous abnormalities

Left superior vena cava (LSVC) can be transected with a rim of left atrium like a right-sided vena cava would be prepared for a bicaval anastomosis. During procurement, all of the superior vena cava and the innominate vein are taken. A standard bicaval approach is performed and the LSVC and innominate vein are connected. LSVC can be tunneled within the recipient right atrium thus a biatrial anastomosis is performed. If the LSVC drains into a coronary sinus, the native heart can be excised keeping the coronary sinus intact and a biatrial anastomosis is performed.

Pulmonary venous anomalies must be corrected allowing unobstructed drainage into native atria. If all pulmonary veins drain into the left atrium, either a biatrial or bicaval connection is possible. If pulmonary venous drainage is mixed or drain into both atria, the donor left atrium can be anastamosed to both recipient atria and a bicaval technique used. Late stenosis is described.

Following a Mustard or Senning and with a right-sided superior vena cava, the right atrium can be removed and a bicaval anastamosis performed

Pulmonary artery hypoplasia and stenosis, stents and systemic-pulmonary shunts

Pulmonary artery (PA) anatomy, if not normal, should be adequately defined by an appropriate imaging technique (echocardiography, angiography, CT angiogram or MRI) at evaluation for transplantation. Any PA stenoses or necessary reconstruction (i.e. take down of a Fontan circuit) can be addressed with donor principal or branch pulmonary arteries, native or donor pericardium or synthetic materials. All systemic-pulmonary shunts must be ligated and divided at the time of transplantation.

Arch anomalies

Transplantation for hypoplastic left heart syndrome or in the presence of any arch abnormalities requires circulatory arrest during the period of arch reconstruction. Neurological damage has been documented especially following 60 minutes of circulatory arrest at 15 to 18°C. However, new techniques of antegrade regional cerebral perfusion (ARCP) avoiding deep hypothermic circulatory arrest (DHCA) seem promising with potential decrease in neurological complications and, through collateral flow, decreased systemic ischemia[100,101] A biatrial approach is preferred since patients are newborns or young infants. All of the aortic arch, PA bifurcation and all of the left atria must be harvested from the donor. While cooling the recipient, the atrial anastamoses are performed. During DHCA or ARCP all ductal tissue is resected to avoid coarctation and the arch anatomosis is performed. The PA anastomosis can be done during the rewarming period.

2. Recommendations: Surgical Technique

1. The surgical technique for heart transplantation where technically feasible should be by the bicaval approach. **(Level B, Class IIa)**

Recipient management

Postoperative care

The same skills and techniques are necessary coming off cardiopulmonary bypass as in more routine cardiac operations, but there are concerns unique to the post-operative heart transplant recipient. The acutely denervated heart is frequently in a slow sinus or junctional rhythm and atrial pacing and/or isoproterenol are frequently needed. Elevated pulmonary vascular resistance with some element of right heart dysfunction is not uncommon. In addition, some degree of ventricular dysfunction as a result of ischemia-reperfusion injury (compounded by the neurohormonal impact of donor brain-death) can lead to acute decompensation of the transplanted heart – compounding the right ventricular dysfunction specifically.[102] This is a life-threatening problem in the early management of these patients. There is center-to-center variability in the management of acute right heart failure. In general, maneuvers should include atrial pacing and/or isoproterenol, inotropic support, maintenance of low filling pressures, avoidance of hypercapnea and acidemia, and pulmonary vasodilation with sodium nitroprusside, milrinone, phenoxybenzamine, and/or nitric oxide. Pulmonary artery stenoses and/or any obstruction at the level of the LA anastamoses (especially in the setting of hypoplastic left heart syndrome) must be ruled out by transesophageal echocardiogram as potentially surgically addressable contributors to right heart failure.

3. Recommendations: Recipient management (Level C)

1. Strategies to manage right heart dysfunction and elevated pulmonary vascular resistance should include atrial pacing and/or isoproterenol, inotropic support, maintenance of low filling pressures, avoidance of hypercapnea and acidemia, and pulmonary vasodilation with sodium nitroprusside, milrinone, phenoxybenzamine, and/or nitric oxide.

Post-surgical complications

The main post-surgical complications are related to the sites of the various vascular anastamoses. Stenoses can develop at the sites of the systemic venous anastamoses (SVC/IVC), pulmonary artery anastamoses (MPA or branch PAs), or the aortic anastamosis/reconstructed aorta. These may all be amenable to intervention in the cardiac catheterization laboratory. Less commonly, the size of the left atrial anastamosis may be a problem. If stenosis is hemodyamically significant and not recognized in the operating room at the time of the post-operative transesophageal echocardiogram, it will likely cause hemodynamic instability in the immediate post-transplant period and require a return to the operating room to revise. Rarely, progressive pulmonary vein stenosis can be a problem, especially if there were pulmonary venous concerns prior to transplant.

Donor Issues

Donor evaluation

An extensive discussion of the issues and challenges surrounding organ donation in Canada is contained within the adult consensus guidelines.[1] Excellent Canadian guidelines have

recently been developed in an expert consensus model to outline medical management of potential organ donors with an aim to maximize organ utilization.[103] Paediatric organ donors are generally previously healthy patients who have suffered irreversible brain death (i.e. trauma, resuscitated near-drowning, sudden intracranial events, etc). Determination of brain death should be made with absolute certainty using accepted criteria.[104] Evaluation of the potential heart donor should include:

1. Blood group. Blood group compatibility (ABO) must exist between the donor and recipient in patients greater than approximately one year of age, depending on the developmental status of the immune system. In infants less than one year of age, ABO-incompatible transplantation may be an option (see ABO-I Transplantation above). Rhesus compatibility is not considered.
2. Donor size. The donor to recipient weight ratio must be considered at the time of the offer. There is much more leeway in the paediatric population than in adults for oversizing the donor heart, especially if the underlying cardiac condition in the recipient has resulted in cardiomegaly. In general, donor weights up to 2.5 times that of the recipient are technically feasible. Oversizing of the donor heart is often desirable in the face of known pulmonary hypertension. The range for undersizing of the donor heart is less wide and not optimal for all patients with a lower limit for the appropriate patients of 80% of the recipient's weight.
3. History of present situation. Knowledge of the mechanism of death is important in interpreting subsequent cardiac testing and clinical information. There is an accumulating body of knowledge on the effect of brain death on heart function.[1,105-107] Accordingly, echocardiographic evidence of mildly decreased function or septal

dyskinesia would likely be acceptable in a patient whose mechanism of death is an intracerebral event compared with a patient with thoracic trauma where the same echocardiogram could be indicative of a myocardial contusion.

4. Past medical history. Particular attention should be given to possible genetic, metabolic or syndromic diagnoses that could have cardiac involvement. Paediatric patients with known medical conditions (neurologic, chromosomal, genetic, etc.) may still be good donors if there is no known cardiac involvement (either myopathic or anatomic).
5. Physical examination. Evidence of thoracic trauma may indicate the possibility of a myocardial contusion. Recent vital signs are good indicators of patient stability and effectiveness of resuscitation in addition to cardiac function.
6. Electrocardiogram. Primary utility is for screening for significant signs of ischemic changes. Non-specific changes are not necessarily a contraindication to organ donation.
7. Echocardiogram. The study should contain both anatomic and functional information. Minor congenital lesions (i.e. ASD, PDA, VSD) are not necessarily contraindications. Consideration of anything other than normal function must be in the context of the status of the potential recipient, donor age, mechanism of death, amount of inotropic support, and projected ischemic time. Echocardiographic functional parameters may need to be repeated when donor clinical status has been optimized.[103]
8. Coronary angiogram. Angiography is almost never a necessity in the paediatric donor population. Heart donors can be any age in extreme situations, since age is

generally less important than size and quality. Older donor age may be acceptable if the coronary risk profile and/or coronary angiogram is normal.[103]

9. Infectious considerations. If there is any history of infection, there should be documentation of appropriate anti-microbial therapy with follow-up cultures on therapy. Information should be collected on the specific micro-organism and anti-microbial sensitivities in the event of concerns about infection in the recipient during the postoperative period. Routine pre-transplant viral serologies should be available to guide organ acceptance and post-transplant prophylaxis as appropriate (see Infections below).
10. Utilization of other organs. In some complex forms of CHD, there may be a need to harvest portions of branch pulmonary arteries, aorta, inferior vena cava (IVC), or the innominate vein to facilitate the anastamoses within the recipient (i.e. hypoplastic pulmonary arteries, dextrocardia with left superior vena cava, isomerism with interrupted IVC and others). If utilization of other organs, especially the lungs, precludes harvesting of the required vessels, the organ may not be able to be accepted for that particular recipient. There is room for discussion amongst the various transplant physicians with regards to the acuity of illness of the different recipients to ensure appropriate placement of the donor organs.

Donor management

Donor resuscitation and support has a significant bearing on the suitability of an organ for transplantation. Appropriate recognition and aggressive management of the cardiovascular effects of brain death are essential to optimize graft function post-transplant. Seemingly marginal donor organs can be made acceptable for transplantation with appropriate interventions

and support with guidance from an experienced intensivist.[105-107] It is appropriate to wait to assess a potential heart donor or to reassess with serial echocardiograms following institution of supportive therapies as outlined below, the recommendations of which have been summarized from a Canadian consensus conference on optimal donor management.[103]

Major hemodynamic changes are induced by brain death that can affect myocardial function. A rise in intracranial pressure causes a catecholamine storm or release of endogenous catecholamines that result in systemic hypertension which is temporary but can be severe.[102] This acute increase in afterload can result in arrhythmias, myocardial ischemia, left ventricular failure and pulmonary oedema[102], and should be aggressively managed with a continuous beta blocker infusion[108] or nitroprusside titrated to effect, as minutes and hours later, there is a decrease in vascular tone and resultant hypotension. If a hypotensive state is predominant, patients should be volume resuscitated to normovolemia prior to institution of hemodynamic supports. Dopamine up to 10 micrograms/kg/minute may be utilized, but doses beyond that probably reflect a need for another agent and/or institution of hormonal therapy (see below). Vasopressin is rapidly becoming the drug of choice due to ongoing concerns about the effect of beta-agonist therapy on the myocardium, and often allows for weaning/minimization of catecholamine support.[109-111] Concurrent with escalating hemodynamic support should be aggressive monitoring including mixed venous oximetry and serum lactate to assess interventions.

Following brain death, free tri-iodothyronine (T_3), thyroxine ($T_{4)}$, cortisol and insulin levels are reduced. A secondary reduction in glucose, pyruvate and palmitate utilization results in the accumulation of lactate and free fatty acids inducing a shift from aerobic to anaerobic metabolism. This shift has been shown to be reversed with the administration of T3.[112,113] A

large retrospective cohort study suggests a benefit of combined hormonal therapy in the organ donor with minimal risk.[114] Combined hormonal therapy includes thyroid hormone, vasopressin and methylprednisolone.

Identification and treatment of diabetes insipidus (DI) is important. DDAVP can be used for treatment in the absence of hemodynamic instability. If inotropic support is required, then continuous vasopressin infusion will address both the hemodynamic need and treat the DI.

Other supportive measures include glycemic control with nutrition and insulin as necessary, management of hypernatremia, red cell transfusion as required for optimal oxygen carrying capacity, and screening and treatment of documented bacterial infections.

Organ procurement

The technique for donor cardiectomy is well-delineated in the surgical literature.[115] A median sternotomy is performed usually simultaneously with the laparotomy for the recovery of the abdominal organs. The heart is examined for any anomalies that may have been missed at the preoperative echocardiogram, including any deterioration in the ventricular function. Prior to harvesting the heart (and the other organs), heparin (300U/kg IV) is administered and a cardioplegia cannula is inserted into the ascending aorta. The superior vena cava is ligated, the inferior vena cava is transected and the aorta cross-clamped and cardioplegia given through the aortic root. The left heart is decompressed by incising the right pulmonary veins. The myocardium is further protected using topical cold saline. Only after all the cardioplegia has been administered without distorting the aortic root, the cardiectomy is completed. Depending on the anatomy of the heart recipient (need for extensive reconstruction in patients with anatomic abnormalities as delineated above) and the heart transplantation technique (Cavo-caval anastomosis vs cavo-atrial), adequate length of pulmonary vein, aorta, pulmonary artery and

caval tissue is harvested. If the lungs are being harvested, the pulmonary veins and arteries are left with the lung specimen.

The heart is then stored in a preservative solution (which can vary by centre), in a series of sterile plastic bags or containers void of air and placed on ice in a cooler to be transported. Much emphasis has been placed on the method of donor organ preservation, especially cardioplegia and preservation solution, and optimal temperature for transport. Despite two decades of investigation, no single preservation regimen has consistent, superior myocardial protection when used within current safe limits of ischemia.

Unlike kidney and liver transplantation, graft function and survival following heart transplantation are significantly decreased by ischemic times of greater than 4 to 5 hours. Differences in survival have been noted when data is stratified for donor heart cold ischemic time with lower percent survival for times of 181 – 300 minutes or > 300 minutes compared with <180 minutes.[4] However, limited numbers of paediatric heart donors force transplantation teams to travel long distances prolonging graft ischemia times. In general, paediatric age donor organs (especially from infants) tolerate longer ischemic times, with reports in the literature of ischemic times over 8 hours that have not adversely affected short or long term outcomes.[116,117] Optimal organ preservation is particularly important in these patients who, in addition to being subject to graft shortages, are often plagued with associated conditions, namely pulmonary hypertension (which requires a normally functioning graft) or anatomic abnormalities (requiring longer operative times).

Donor allocation

Routine donor allocation as it currently exists in Canada is outlined in the adult consensus guidelines.[1] In brief, the current status system in Ontario, which was developed to allow the patients at highest risk and with greatest need to take priority, is as follows:

Status 1	Waiting at home
Status 2	Hospitalized for complication of heart disease
Status 3	Ward care + ventricular assist device or inotropes
Status 3.5	ICU care + PA catheter + high dose/multiple IV inotropes
Status 4	ICU care + mechanical ventilatory or circulatory support

Currently, hearts are allocated according to this consensus status grading, blood group, body size, and time on the waiting list, and donor region. The current status system poses some challenges for the paediatric and the adult congenital population as it is based on a relatively uniform population with a well-documented and predictable clinical course of deterioration that is reflected in this system. However, the clinical deterioration that this reflects is not that experienced by patients with CHD whose challenges are primarily anatomic and/or cyanosis-related as opposed to that of progressive myocardial dysfunction. In partial recognition of this, any paediatric patient less than six months of age is automatically listed at atleast Status 3.

Taking it one step further, the United Network for Organ Sharing (UNOS) in the US has within its Organ Distribution policy separate listing criteria for the paediatric age group (policy 3.7.4). In addition, policy 3.7.5 allocates adolescent donor hearts to a paediatric recipient prior to an adult recipient in recognition of the data supporting better long term outcomes for adolescent recipients receiving adolescent hearts.[118] This has recently been reflected in changes to the organ allocation algorithm within Ontario with hearts from donors less than 18 years of

age being offered to recipients less than 18 years of age first. In Canada, further consideration needs to be given to a parallel listing strategy for paediatric patients and for adult patients with CHD that more reflects the clinical course of deterioration in this patient population, allowing those at highest risk and therefore greatest need to take priority as is the basic philosophy behind the consensus status system.

4. Recommendations: Donors

1. Donor evaluation: thorough evaluation of the potential organ donor as outlined above is essential to maximize use of all possible available organ donors and to optimize outcomes in the organ recipient. **(Level C, Class I)**

2. Donor management: aggressive resuscitation and ongoing management under the guidance of experienced intensivists or transplant physicians is essential to maximize use of all possible donor organs (especially those that are marginal) and to optimize outcomes in the organ recipient. **(Level C, Class IIa)**

3. Organ procurement: donor organs should be procured by a team experienced in optimal organ assessment, harvesting, preservation and transport. **(Level C, Class I)**

4. Ischemic Times: Optimally should be less than 5 h because longer ischemic times are a risk factor for adverse short and long term outcomes. However, prolonged ischemic times should be assessed on an individual donor basis, taking into account donor age and baseline cardiac function, as infant and younger donor organs tolerate longer ischemic times. **(Level C, Class 1)**

5. Status system: Consideration needs to be given to a parallel listing strategy for paediatric patients and for adult patients with CHD that more reflects the clinical course of deterioration

in this patient population, allowing those at highest risk and therefore greatest need to take priority as is the basic philosophy behind the consensus status system. **(Level C, Class IIa)**

Sensitized Patients

Screening panel reactive antibody (PRA) testing is performed on patients prior to transplantation in an effort to minimize the risk of antibody-mediated allograft rejection post-transplantation. PRA tests for the presence of preformed HLA antibodies to a random panel of donor lymphocytes. High PRA values (>10%) are associated with an increased incidence of rejection and reduced survival post-cardiac transplantation.[119,120] Previous open heart surgeries, especially those necessitating the placement of homograft material, can lead to an increased incidence of elevated PRAs. There are several reports of successful heart transplantation in sensitized patients.[121,122] The pre-transplant preparation of these patients has varied and, though there is agreement that there should be some form of intervention directed at decreasing preexisting antibody, there is no consensus amongst centres. A Canadian consensus document addressing this is in progress and due to be published in mid to late 2005. The various strategies to try to lower antibody levels in sensitized patients include plasmapheresis, intravenous immunoglobulin (IVIG), cyclophosphamide, rituximab and anti-metabolite treatment prior to transplantation.[123-125] In some high-risk cases, prospective donor/recipient cross-matching or a "virtual cross-match" may be necessary to identify donor/recipient pairs that may be at risk of hyperacute or early vascular rejection.

5. Recommendations: Sensitized patients

1. All patients should undergo PRA testing as part of the pre-transplant assessment with repeat testing if there is exposure to any potentially sensitizing event (surgery, blood product transfusion) prior to transplantation. **(Level C, Class I)**
2. Sensitized patients should be considered for pre-transplant interventions aimed at lowering the antibody levels including a combination of IVIG, cyclophosphamide, antimetabolites, rituximab and/or plasmapheresis under the guidance of an experienced transplant physician with a plan for management in the post-transplant period should the donor-specific cross-match be positive. **(Level C, Class IIa)**
3. Prospective donor/recipient cross-matching should be considered in highly sensitized patients. **(Level C, Class IIa)**

IMMUNOSUPPRESSIVE THERAPY

Immunosuppressive drug therapy is the cornerstone upon which post-heart transplantation management is based. The goal is to prevent graft rejection while minimizing side effects and toxicities. There has been a large increase in the number of IS agents available (Table 3) and they are extensively reviewed in the adult consensus guidelines.[1] Comments here will be restricted to paediatric-specific considerations. Importantly, virtually none of these therapies has been studied in randomized, controlled trials in paediatric heart transplant recipients, and most are only approved for use in adult kidney and liver transplantation. There is no consensus on the optimal immunosuppressive drug regimen, with even more variability

amongst centres doing paediatrics compared with adult heart transplants. In the annual report from ISHLT, expanded data are now given on IS medication use.[3] The one consistent agreement is the need for an individualized approach based on each patient's age, risk factors, rejection history, and profile of side-effects and toxicities. There are several recently published reviews of IS in the paediatric population.[126-128]

Table 3: Immunosuppressive agents

Generic Name	Proprietary Name	Type	Clinical Use
Prednisone		Steroid	Maintenance therapy Rejection treatment
Cyclosporine	Neoral [Novartis]	Calcineurin Inhibitor	Maintenance therapy
Tacrolimus	Prograf [Fujisawa]	Calcineurin Inhibitor	Maintenance therapy
Azathioprine	Imuran	Purine anti-metabolite	Maintenance therapy
Mycophenolate Mofetil	CellCept [Roche]	Purine biosynthesis inhibitor	Maintenance therapy
Sirolimus	Rapamune [Wyeth]	TOR inhibitor	Maintenance therapy
Everolimus (RAD)	Certican [Novartis]	TOR inhibitor	Maintenance therapy
Rabbit ATG	Thymoglobulin [Genzyme]	Rabbit polyclonal antibody	Induction therapy Rejection treatment
Basiliximab	Simulect [Novartis]	Antibody to IL-2 receptor	Induction therapy
Diclizumab	Zenapax [Roche]	Antibody to IL-2 receptor	Induction therapy

Induction Therapy

As noted above, agents used for induction therapy, including polyclonal (ALG, ATG, ATGAM, RATG) and monoclonal antibodies (OKT3, basiliximab, dacluzimab), are extensively reviewed in the adult consensus guidelines. As with adults, whether induction therapy is necessary or advantageous remains controversial, with many single centre retrospective studies showing both positive and negative outcomes using very varied protocols.[1] Analysis of registry data from ISHLT continues to show an increasing percentage of patients receiving induction therapy (35% in 2001, >50% in 2003).[3] Two recent paediatric studies using rabbit antithymocyte globulin (Thymoglobulin) have been published with both showing excellent patient and allograft survival with a low risk of post-transplant lymphoproliferative disorder (PTLD – see below).[129,130] However, other centres have achieved similar results without induction therapy. One strategy is to use induction therapy in specific groups of patients; a) those at a high risk of rejection, or b) those in whom delaying the introduction of more routine immunosuppression or utilizing lower therapeutic levels may be desirable, e.g. patients with renal dysfunction. The efficacy and safety of Thymoglobulin in comparison to either of the IL-2 receptor blockers, basiliximab or dicluzimab, is unknown as there have been no paediatric studies. Therefore, the use of induction therapy is centre-specific and dependent on clinical experience and preferences.

6. Recommendations: Induction Therapy

The use of induction therapy is centre-specific and dependent on clinical experience and preferences. Induction therapy with polyclonal antibodies may be beneficial in certain groups of patients (high risk of rejection, significant renal dysfunction). **(Level B, Class IIa)**

Maintenance Therapy

As indicated above, combinations of IS agents can be used in an individualized approach in order to achieve the goal of none to minimal rejection while minimizing side-effects and toxicities. The most commonly used agents include steroids, calcineurin inhibitors, and purine anti-metabolites (Table 3). The mechanisms of action of all of these agents are extensively reviewed in the adult consensus guidelines and recent review articles.[1,127,128,131-134] There is an ongoing interest in steroid-free IS regimes to reduce steroid-related morbidities. However, data from the ISHLT database demonstrates that most centres are still using steroid therapy with the number of patients receiving steroids decreasing with time.[3] Though it is feasible to withdraw steroids and/or even avoid them completely in the paediatric heart transplant population, it remains a challenge to identify the high-risk patients and the optimal IS regimen to facilitate steroid withdrawal or avoidance, whilst minimizing other IS morbidities, especially renal dysfunction.[135-138]

Calcineurin inhibitors remain the mainstay of maintenance IS regimens. Therapeutic drug monitoring is essential for optimal use of both cyclosporine and tacrolimus. Clear knowledge of the side-effect profiles and the multiple potential drug interactions of both agents are essential. Both the ISHLT and PHTSG databases reveal a trend towards the use of tacrolimus.[3,4] This is not evidence-based. There is only one randomized trial of tacrolimus versus cyclosporine in paediatric heart transplant recipients in which a) both regimens are efficacious immunosuppressive agents in paediatric heart transplant recipients, b) the incidence of drug-related adverse events was similar, though their spectrum was different, c) there was no difference between groups in incidence of allograft rejection and graft or patient survival, and d)

conversion from cyclosporine to tacrolimus was useful for dealing with refractory rejection.[139] All other reports in the literature on calcineurin inhibitor use in paediatric heart transplant recipients are small numbers, retrospective and single centre. Therapeutic drug monitoring as an assessment of drug exposure is important for both calcineurin inhibitors. Though there is increasing literature in the adult population with regards to C2 monitoring for cyclosporine, there are no studies in the paediatric heart transplant population and the utility and appropriate target levels remain to be determined.

In 2003, both the ISHLT and PHTSG databases revealed a trend towards the use of mycophenolate mofetil as the primary antimetabolite agent in >50% of patients within the first year post-transplant.[1,3] Again, there is minimal literature about the use of MMF in the paediatric heart transplant population, but what there is supports its use as an effective agent for maintenance IS, for treatment of rejection, for potentially facilitating a steroid-free regimen, and advocates for therapeutic drug monitoring.[138,140]

The introduction of the TOR inhibitors like sirolimus to IS regimens has opened up even further possibilities for steroid withdrawal or avoidance and for minimization of IS agent morbidities, especially renal dysfunction. There is very little literature on the use of sirolimus in the paediatric heart transplant population.[137,141] In a recent retrospective review, sirolimus in combination with tacrolimus and MMF was a) an effective adjunct immunosuppressive agent for ameliorating moderate to severe acute rejection episodes and moderate to severe kidney dysfunction, b) facilitated the lowering of tacrolimus dose and target levels in all patients without a concurrent increase in rejection, and c) appeared to have an acceptable side-effect profile. Though therapeutic drug monitoring was used in the retrospective study, the optimal target trough levels in paediatric heart transplant recipients still need to be established.

7. Recommendations: Maintenance Therapy (Level C, Class I)
1. The optimal paediatric heart transplant immunosuppressive regimen remains to be determined. IS regimens should be tailored to the needs of each individual patient, taking into consideration patient age, time post-transplant, risk factors, rejection history, and profile of side-effects and toxicities.
2. Steroid withdrawal or avoidance protocols remain desirable, though the optimal means to achieve this remains to be elucidated and is currently centre and physician-dependent. 3. Therapeutic drug monitoring as a means of assessing drug exposure is strongly recommended for both cyclosporine and tacrolimus. At the present time, trough levels remain the method of choice, though C2 monitoring is currently being explored in the paediatric population. 4. Therapeutic drug monitoring for mycophenolate mofetil and sirolimus may be beneficial for the optimal dosing to reduce rejection and minimize toxicity.

POST-TRANSPLANT ISSUES/COMPLICATIONS

Post-transplant issues in the paediatric population are somewhat different than in adults. Care of children post-heart transplantation must take into consideration physical growth and multi-system development, stage of immunologic development, intellectual, emotional and social maturation, educational activities, and other paediatric quality of life parameters. Each one of these aspects and how they are considered within the management plan can affect the morbidities

and mortalities post-heart transplantation. The hallmark of post-transplant care is meticulous long-term attention to details with ongoing surveillance and a high index of suspicion for transplant-related problems.

Post-transplant complications in the adult congenital population are not significantly different from those of the adult population in general, and are well outlined in the adult consensus guidelines.[1] This section will concentrate primarily on the issues unique to the paediatric population.

Rejection

Rejection is the process of destruction of genetically foreign material by the host's immune system. The severity and timing depends on the degree of genetic dissimilarity between donor and recipient. Although acute graft rejection remains an important potential cause of mortality and morbidity post-transplant, its incidence and impact on graft survival has decreased over the years due to improved IS regimes. By 6 months post-transplant, 61% of patients have had at least one episode of acute cellular rejection.[142] The majority of transplant recipients will have at least one episode of rejection in the first year post-transplant, but are usually asymptomatic and identified on routine surveillance endomyocardial biopsy (EMBx), are easily treated, and do not result in significant morbidity and mortality. Of patients alive at one year, 27% will experience an episode of late rejection within 3 years.[142] Mortality among patients with late rejection is significantly higher than those without late rejection.[143] Late rejection episodes are also more often associated with hemodynamic compromise requiring inotropic support. Rejection with hemodynamic compromise is associated with a higher incidence of graft failure and mortality, with only 50% of patients alive at one year after an episode.[144] Rejection

often recurs with only 33% of patients with one episode remaining free of subsequent episodes at 5 years following the event.[145] Acute rejection can lead to graft dysfunction, graft failure, and death.[146,147] It is the leading cause of death during the first 5 years after heart transplantation,[148,149] producing a rejection-related mortality of about 7% over 5 years. Fatal rejection is most likely to occur in the first month after transplant. As many as 25% of the paediatric transplant recipients will have acute rejection that is either recurrent or does not resolve despite standard immunosuppressive agents. Therefore, reducing the overall incidence and/or severity of rejection remains an important therapeutic goal in paediatric cardiac transplant recipients.[150]

Types of rejection

There is an extensive discussion of the types and mechanisms of rejection in the adult consensus guidelines.[1] These are similar for the paediatric population and include:

1. Hyperacute rejection due to the presence of pre-formed antibodies of the recipient to the donor graft. Histology reveals antibody and complement deposition and polymorphonuclear lymphocyte infiltration. It can be pre-empted by prospective donor-specific crossmatch and blood group matching, but cannot easily be reversed. Less than 1% of all heart grafts are lost due to hyperacute rejection.
2. Acute cellular rejection initiated by antigen-presenting cell contact with T helper lymphocytes. This is the most common type of rejection seen post-transplant.
3. Antibody-mediated humoral or vascular rejection which is a microvascular immune-mediated injury in the absence of cellular infiltrate and necrosis.

Acute graft dysfunction occurs in the absence of typical histologic features of acute cellular rejection. This is a rare form of rejection and can be difficult to diagnose, and needs to be corroborated with immunoflourescence staining for deposition of immunoglobulin and complement.[4]

Risk factors for rejection

It is difficult to identify risk factors for rejection pre-transplant other than prior sensitization (see Sensitization above). Not much information is available regarding the factors which predispose to rejection in children compared to adults. It is not very clear whether recipient age is a risk factor for rejection. Younger age has been identified as a predictor of earlier rejection[151,152], but a multivariable analysis from PHTS identified older age among paediatric patients as risk factor for first rejection and cumulative rejection within first 6 months post-transplant.[153] The effect of HLA mismatches has not been well-studied. Donor/recipient gender mismatch was identified as a probable risk factor. Recipient black race may also predispose to increased rejection.[153] Cytomegalovirus infection after heart transplant may predispose to rejection.[154] Risk factors for late rejection, rejection with hemodynamic compromise, and recurrent rejection include older recipient age, black or Hispanic race, more frequent early rejection, greater than one episode in the first year post-transplant, and shorter time since a previous rejection episode.[143-145]

Diagnosis of rejection

In general, most episodes of acute rejection are asymptomatic. Clinical signs and symptoms do not usually occur until rejection is advanced. When symptomatic, paediatric patients can present with nonspecific symptoms including lethargy, fever, and decreased feeding. Clinical signs can include tachycardia, tachypnea, frequent premature beats, or an extra heart

sound.[142] As indicated above, hemodynamically compromising rejection can present with signs of ventricular dysfunction including congestive heart failure and hypotension with decreased cardiac output.

The currently accepted "gold standard" for assessment of cardiac allograft rejection is by endomyocardial biopsy (see below). Other noninvasive methods for screening for rejection are outlined in the adult consensus guidelines.[1] In the paediatric population, serologic markers and echocardiography have been explored, but there is no noninvasive method that is felt to be reliable enough to replace the use of EMBx for rejection surveillance.[155,156]

Endomyocardial Biopsy (EMBx): As discussed in the adult consensus guidelines, percutaneous EMBx remains the gold standard for the diagnosis of cardiac allograft rejection in most centres.[1] Though utilized by the majority of paediatric heart transplant centres across North America, there is considerable variability among programs with regards to the frequency of EMBx in the paediatric population. Challenges include the need for a general anaesthetic (except in the adolescent age group), small size (especially the infant population), increased incidence of venous anastamosis stenoses, and increased incidence of technical challenges including unusual venous anatomy and venous thromboses with loss of routine vascular access. There are no clinical trials looking at the optimum timing and frequency of EMBx. In general, EMBx is performed initially within the first 7-14 days with a gradual increase in the time interval between biopsies. Infant recipients may not be biopsied for the first month or until a predetermined weight is achieved, and then subsequently much less frequently than older patients. In the current era with tailored immunotherapy, each patient can be assessed individually with regards to need for and frequency of EMBx for adjustment of IS. In the absence of evidence of graft dysfunction or major changes in IS, and with a relatively benign

rejection history, there is a trend to decreased biopsy frequency with approximately 2-3 biopsies per year the second and third year post-transplant and 1-2 biopsies per year the third to fifth year post-transplant. In some cases with a very benign rejection history, the option exists for cessation of routine EMBx surveillance, though there are centres in North America that continue routine surveillance EMBx indefinitely.

There are several histologic grading systems for interpretation of the EMBx, but the most commonly accepted and applied is that developed by the ISHLT for standardization of reporting and to guide therapy.[157]

Echocardiogram: In acute rejection, the echocardiogram, though generally unremarkable may show signs and changes that reflect an increase in left ventricular mass, impairment of systolic and diastolic function of either ventricle, pericardial effusion and/or new or increasing valvar insufficiency.[156] Changes can be relatively subtle, and individual comparison with prior studies is essential if rejection is suspected by echocardiography, with each patient serving as his or her own control.

Treatment of acute rejection

The approach to the treatment of acute rejection is very similar to that of adult heart transplant recipients.[1] In general, asymptomatic mild rejection (ISHLT 1A or 1B) does not require treatment. If relatively early post-transplant (within 2 months), a follow-up EMBx should be scheduled sooner to look for signs of progression, especially if induction therapy was used. The importance of an ISHLT 2 (focal, moderate rejection) result remains the subject of much controversy and should be considered in the context of an individual patient's biopsy history. If it is relatively early post-transplant, consideration should be given to augmentation of immunosuppression with high dose intravenous steroids and optimization of maintenance

immunosuppression levels. Beyond six months post-transplant, generally ISHLT 2 rejection is treated similarly to a 1A or 1B, with repeat biopsy (timed when deemed clinically appropriate), with or without changes in baseline immunosuppression (i.e. optimization of levels for weight gain, etc.). **The 2004 proposed revised ISHLT biopsy grading system no longer separately categorizes Grade 2, but instead categorizes rejection as mild (1A, 1B, 2), moderate (3A) or severe (3B, 4).**

A grading of ISHLT 3A or 3B (moderate rejection) requires some intensification of immunosuppression. Usually the patients are asymptomatic with normal hemodynamics and a normal echocardiogram (see above). Traditionally, high dose intravenous steroids have been used (once a day for a three day period) in addition to modification of baseline immunosuppression therapy. There is clinical and anecdotal evidence that oral pulse steroids may be used effectively in these circumstances as well.[158,159] For moderate rejection within the first month post-transplant and/or moderate rejection associated with hemodynamic compromise, in addition to intravenous pulse steroids, consideration should be given to the use of cytolytic therapy (anti-T cell antibodies such as anti-thymocyte globulin). Follow-up biopsies should be performed within 2-6 weeks after treatment to monitor rejection status. The timing, again, can be individualized based on timing post-transplant, severity of rejection, presence or absence of hemodynamic compromise, past rejection history and concurrent circumstances that may be contributing (i.e. non-compliance, concurrent or recent viral infections, recent subtherapeutic IS levels, etc.). Severe rejection (ISHLT 3B, 4), is rare, but should be aggressively treated with intravenous steroids, cytolytic therapy, augmentation of baseline immunosuppression and circulatory support as required.

Patients with more recalcitrant rejection histories need individualized attention. By definition, persistent rejection is defined by a biopsy grade of 3A or greater present on two or more consecutive biopsies. Steroid-resistant rejection exists with ongoing rejection following two consecutive episodes treated with steroids. Outside of these definitions are the patients with ongoing rejection of varying severity over time, with few or no periods of absent or mild rejection. Therapeutic options include intravenous steroids and cytolytic therapy, changing calcineurin inhibitors (CyA and Tac), changing anti-metabolite drugs (Aza and MMF), using an mTOR inhibitor (sirolimus), and, in extreme cases, using cyclophosphamide or methotrexate. Non-pharmaceutical options include total lymphoid irradiation (TLI), plasmapheresis or photopheresis for which there is limited paediatric experience.[160]

Treatment of humoral or vascular rejection (antibody-mediated rejection)

Microvascular rejection may be present in the absence of a cellular infiltrate and is antibody-mediated. Histologic features include endotheliitis with complement and immunoglobulin deposition. This type of rejection can be severe, difficult to treat, and has a worse prognosis than acute cellular rejection. Previously, there has been no standardized way of diagnosing and reporting this form of rejection, but the 2004 proposed revised ISHLT biopsy grading system does include criteria for pathologic diagnosis and immunostaining for antibody mediated rejection. Treatment including high dose steroids, IVIG, plasmapheresis, and cyclophosphamide has been associated with an improved outcome (survival and graft function).[161,162] More recently, MMF and rituximab have been used to treat humoral rejection with reported short-term success.[125]

8. Recommendations: Rejection

Diagnosis

Clinical

1. Majority asymptomatic

2. Symptoms: malaise/lethargy, fever, feeding intolerance/decreased appetite, exercise intolerance, new or increased frequency of premature contractions, clinical findings of congestive heart failure

Testing

1. Catheterization: elevated atrial and/or ventricular end-diastolic pressures

2. EMBx remains the gold standard for surveillance of rejection. There should be individualized "routine" scheduling as per clinical situation (see text). **[Level C, Class IIa]**

3. The ISHLT standardized grading system for histologic assessment of EMBx should be used for diagnosis of grade of rejection to guide therapy. **[Level C, Class I]**

Treatment

1. Mild (ISHLT 1A/1B) and focal moderate (ISHLT 2) rejection usually does not require specific therapy. Consideration may be given to an increase in maintenance IS (steroid, calcineurin inhibitor, MMF dose). **[Level B, Class IIa]**
2. Moderate (ISHLT 3A/3B) and severe (ISHLT 4) rejection should be treated with intensified IS. Asymptomatic moderate rejection can be managed with oral pulse steroids. Early post-transplant moderate rejection usually requires intravenous steroids. Severe rejection or any rejection with hemodynamic compromise usually requires intravenous steroids and/or cytolytic therapy. Maintenance IS should be adjusted concurrently with the acute intensive treatment. **[Level B, Class IIa]**

3. Follow-up EMBx should be done within 2-6 weeks as clinically indicated to assess for progression and to evaluate efficacy of treatment. **[Level B, Class IIa]**
4. Persistent rejection despite treatment with steroids can be managed with a change in calcineurin inhibitor or anti-metabolite agent, consideration of an mTOR inhibitor, or, in extreme circumstances, cyclophosphamide or methotrexate. **[Level C, Class IIa]**
5. Treatment of humoral rejection can include some combination of intravenous steroids, plasmapheresis, IVIG, MMF, cyclophosphamide, and rituximab. **[Level C, Class IIa]**

Transplant Coronary Artery Disease

Background

Transplant coronary artery disease (TCAD) is a diffuse, chronic vascular injury to the graft. TCAD differs from classical coronary artery disease in that it is diffuse, involving all levels of the vascular tree including veins, arteries and great vessels. Graft ischemia results from circumferential thickening of the vascular intima. Early clinical signs of TCAD are almost non-existent in heart transplant recipients. Since the transplanted heart is denervated (i.e. not "connected") to the nervous system, the patients may not experience characteristic chest pain (angina), even in the face of significant myocardial ischemia. The diagnosis of TCAD can be difficult with first clinical manifestations being symptoms of advanced disease including congestive heart failure, ventricular arrhythmias and death. TCAD is a major limitation to long-term survival after paediatric heart transplantation and the most common indication for retransplantation.[22,163,164] After the first year post-transplant, TCAD is the commonest cause of

morbidity and mortality, yet it still occurs much less frequently than in adult patients, especially in younger paediatric recipients.[3]

Pathogenesis

The pathogenesis of TCAD is multifactorial and includes both immune and non-immune-related factors. Rejection episodes during the first 6 months after transplantation and rejection with hemodynamic compromise after the first year have been identified as predictors of subsequent development of TCAD.[165,166] The development of TCAD is associated with donor-specific alloreactivity to vascular endothelium.[167] It is promoted by a number of cytokines and growth factors.[168] There is probably some relationship between number of acute cellular rejection episodes and the risk for TCAD.[169-174] Other immunologic risk factors for TCAD observed in adult transplant recipients are likely to be related in the paediatric population as well. Some of these factors are donor/recipient HLA mismatch, endothelial activation, and presence of antibodies against donor endothelium.[167-169]

Many non-immune factors may contribute to the development of TCAD. Specific risk factors for paediatric patients have not been identified and evaluated in a large prospective study. Older donor age, donor male gender, donor hypertension, recipient male gender and recipient black race are recognized risk factors for TCAD in the adult population, but their role in the paediatric population is largely unknown.[175] Other non-immune-related associations include CMV[154,176,177], possibly Chlamydia[178,179], hypercholesterolemia[180-183], smoking[172,184], hypertension[184], elevated homocysteine[185,186], elevated troponin T levels[187], and cumulative prednisone dose.[173]

Hyperlipidemia is common after heart transplantation.[180,181] This problem extends to the paediatric population as well, and may contribute to TCAD as noted above.[180-183] The major

causes of dyslipidemia in heart transplant patients are genetic predispositions, high-fat diets and immunosuppressive medications (especially cyclosporine and sirolimus). Most patients gain excess weight after transplantation even though they were below ideal body weight previously. Steroids are frequently blamed during the first year post-transplantation. Some patients have a history of familial hyperlipidemia that will contribute to the post-transplant lipid perturbations, and family members should be screened appropriately.

Prevalence

Depending on the methods used for surveillance, the prevalence of TCAD in children is 12% to 24% at 1 year and 18% to 43% at 3 years after transplant.[188-191] Data obtained from PHTS indicates an incidence of TCAD of 0.4% per year based on angiographic detection, and a risk of death from this complication of only 2.1% during the first 5 years after transplantation.[148] However, the prevalence of TCAD by intravascular ultrasound (IVUS) exceeds 70% at 5 years after transplant.[192]

Diagnosis

Although classical symptoms of coronary disease such as angina often do not occur due to cardiac de-nervation, they can occur in a small percentage. Often symptoms are of anginal equivalents, e.g. shortness of breath. When cardiac symptoms do develop, they usually represent advanced disease, e.g. congestive heart failure, myocardial infarction, arrhythmias and sudden death. Since the majority of TCAD is asymptomatic, it is routinely screened for in most centres. Detection of asymptomatic TCAD is highly dependent on the aggressiveness of the screening protocol. This can be a challenge for the paediatric population as a number of the potential screening modalities are limited by age, size, degree of cooperation, and/or need for sedation or general anaesthesia.

Non-invasive testing

Dobutamine stress echocardiography (DSE) is a promising non-invasive technique for detecting TCAD. The use of DSE has been advocated in adult heart transplant recipients for routine surveillance for TCAD[193]; in some centers even replacing routine angiography. In one study, DSE was compared to coronary angiography with a sensitivity of 72% and a specificity of 80%.[190] Several studies carried out in adult patients now predict a relationship between an abnormal DSE and TCAD-related events.[193-196] Preliminary studies in children have supported the feasibility and safety of DSE in the paediatric population, in addition to providing preliminary evidence for a role in identifying children with TCAD.[190,197,198] Other than safety and feasibility, one advantage of DSE over angiography (see below), is the provision of functional information (i.e. the impact of the presence of TCAD on graft function) that can be followed serially for progression. DSE may be applied to all age groups and developmental stages, though younger patients and those who are unable to cooperate may require a general anaesthetic. The interpretation of DSE should be done by an experienced echocardiographer. DSE is not currently available in all paediatric centers in Canada.

Supportive evidence for the presence of ischemia may be obtained by exercise testing and nuclear medicine scintigraphy[187], but the application of these testing modalities is limited to older, cooperative patients and abnormalities are manifested, if at all, at relatively advanced stages of the disease. The combination of DSE and nuclear medicine scintigraphy is a possibility for the smallest children in whom angiography is not an option (i.e. due to technical issues such as vascular access).

Invasive testing

The types of angiographic coronary lesions seen in children are similar to those in adults. They include focal lesions, diffuse concentric lesions and abrupt obliteration with loss of distal branches. Historically, the diagnosis of TCAD has relied primarily on selective coronary angiography. Angiography for the diagnosis of TCAD is now being questioned as the "gold standard" as it tends to underestimate TCAD compared with pathology or intravascular ultrasound.[191,194,195] In addition, angiography provides minimal information on the impact of TCAD on graft function.[191] Finally, once transplant coronary artery disease is evident angiographically, short-term mortality is high.[194,195] The frequency of routine angiography varies from center to center. In general, a baseline angiogram is done at approximately one year post-transplant (if patient size and vascular access are not limiting factors), and then annually or biannually thereafter. In the youngest and smallest of patients, repetitive angiography may be technically challenging.

Intravascular ultrasound (IVUS), in conjunction with coronary angiography, has the greatest sensitivity for the identification of and to study the progression of TCAD, and is routinely used in many adult transplant centers. IVUS has been safely used in the older paediatric population.[192] However, it may add cost, time and potential morbidity to screening protocols, while the clinical benefit of the routine application remains unproven.[199] The application of IVUS in the paediatric population is presently limited to older children due to the size of the available IVUS catheters. In some centres, IVUS is used in selected patients with clinical indications and/or specific risk factors for the presence or development of TCAD. Its use is not widespread amongst paediatric centres at the present time due to the aforementioned considerations and availability in individual centres.

9. Recommendations: Screening and Diagnosis of TCAD

1. Patients should be screened annually or biannually for the presence of TCAD. The modality used for screening may be individualized by centre according to expertise, test availability, and applicability to individual patients. **[Level C, Class IIa]**
2. Coronary angiography, when not limited by weight or vascular access, should be undertaken at one year post-transplant and then annually or biannually thereafter, depending on the frequency and results of non-invasive testing. **[Level C, Class IIa]**
3. The role of IVUS remains unclear and, at the present time, is used primarily as an adjunct to angiography in selected patients in centres where it is available. **[Level C, Class IIa]**

Treatment

Treatment options for TCAD are very limited. As noted above, recent data from IVUS studies have demonstrated some degree of intimal proliferation in 70% of patients at 5 years post-transplant.[192] Degree of intimal proliferation (or luminal narrowing) can vary from mild to severe. Of key importance in the milder spectrum of disease is the functional significance on the graft. Once TCAD is determined to be present, some centres have tried immunologic modulation to attempt to promote regression or delay progression.[200] Newer IS agents (see above) have purported action on smooth muscle cell proliferation with possible effects on the progression of TCAD, and consideration may be given to utilizing these medications (i.e. mTOR inhibitors - sirolimus, everolimus). Attempts should always be made to modulate non-immune factors as well including hyperlipidemia, hypertension and obesity.

In the adult population, percutaneous transluminal angioplasty (PTCA) and/or stenting for discrete lesions has been successfully performed.[1] However, the majority of patients are not amenable to these techniques due to the diffuse nature of the disease. Similarly, coronary artery bypass grafting (CABG) has also been successfully performed in a limited number of patients, but has a very limited role.[1] There has been very limited reported experience with the use of coronary intervention procedures for palliation of CAD in the paediatric transplant population. Shaddy, et al., reported on three patients who safely underwent angioplasty, stent placement and rotational atherectomy, respectively.[201] None of these procedures has been performed in large number of patients and the long-term outcomes are unknown. An added factor in the paediatric population is that patient size often precludes any of these interventions.

From a supportive, medical therapy point-of-view, medical management of the sequelae of TCAD (eg. myocardial ischemia) should include standard of care treatment as clinically indicated such as aspirin, anti-anginal medications (eg. nitrates – short or long acting), beta blockers, anti-hypertensives. or others. There are some centres that advocate the use of automatic implantable cardiac defibrillators (AICD) given the risk of sudden death due to arrhythmias in this patient population, but opinions vary. At a minimum, standard criteria for implantation should be applied.

Despite recent advances in graft preservation, immunosuppression and prevention of TCAD, re-transplantation is the only treatment proven to achieve long-term recipient survival after development of TCAD.[202] Once the diagnosis of TCAD is made, the decision of offering re-transplantation should be individualized on the basis of the extent of disease, evidence of graft dysfunction or inducible ischemia.

10. Recommendations: Treatment of TCAD

1. For mild or moderate TCAD, consideration may be given to alternate forms of IS, in addition to intervention on non-immune risk factors (i.e. hypertension, hyperlipidemia, and obesity), to modulate the progression of TCAD. **[Level C, Class IIa]**
2. In the rare circumstance in which coronary artery lesions are severe enough and amenable to coronary intervention or surgical revascularization, this should be undertaken. **[Level C, Class IIa]**
3. Once a diagnosis of moderate to severe TCAD is established, consideration should be given to re-transplantation. **[Level C]**

Prevention

Lipid-lowering therapy

Lipid-lowering therapy, specifically HMG-CoA reductase inhibitors (i.e. pravastatin, or "statins"), have been shown to play a role in the prevention of TCAD. Kobashigawa et al, randomly assigned adult patients early post-transplant to pravastatin (n=47) or no pravastatin (n=50).[203] At one year follow up, the use of pravastatin reduced the incidence of acute rejections associated with hemodynamic compromise, improved one year survival, and reduced the development of TCAD. This was independent of cholesterol level. Therefore, the benefit of HMG-CoA reductase inhibitors goes beyond cholesterol reduction. Similar findings have been shown for a combination of low-cholesterol diet and simvastatin post-transplant.[204] Investigations of the lipid lowering effect among paediatric heart transplant subjects have been limited but have demonstrated both safety and efficacy of pravastatin and atorvastatin.[205,206] Mahle et al have recently retrospectively demonstrated an association between the routine use of

pravastatin and a lower risk of TCAD in the paediatric population.[207] The long-term outcome of statin use in paediatric transplant patients is unknown. For resistant hyperlipidemia, conversion from cyclosporine to tacrolimus could be considered.[208]

Though the recommendation in the adult consensus guidelines is for all patients to receive either pravastatin or simvastatin after cardiac transplantation regardless of baseline LDL, there is not enough data in the paediatric population to make the same statement.[1] In addition, there is no data in ages younger than adolescence as to the pharmacokinetics, dosing, and side-effects of these drugs. Finally, there are no commercially available liquid preparations of the statins which makes administration of these agents challenging in the younger age group. Nevertheless, all patients at any age who are hyperlipidemic should be treated with a combination of dietary management, modification of immunosuppression if possible, and lipid-lowering therapy. Consideration should be made to follow the adult consensus guidelines for all adolescent recipients.

Calcium Channel Blockers and ACE inhibitors

There is data in the adult literature that the use of the calcium channel blocker, diltiazem, may also have a benefit in the prevention of TCAD, but no long term data is yet available.[209-211] There is very preliminary data for a role of angiotensin converting enzyme inhibitors (ACEI) in reducing vascular intimal hyperplasia.[210] There is limited experience with the use of pharmacologic interventions in paediatric transplant recipients. It is unknown if those interventions may produce similar benefits in children as in adults. The long-term impact of this pharmacologic approach remains to be proven.

11. Recommendations: Prevention of TCAD

1. Patients with modifiable non-immune risk factors should be intervened upon including hyperlipidemia, obesity, hypertension, etc. **[Level C, Class IIa]**
2. The impact of statin therapy, ACEI, and calcium channel blockers on the progression of TCAD in the paediatric population is largely unknown. If treatment is required for hyperlipidemia or hypertension, consideration should be given to utilizing these agents because of the possible benefits on reducing TCAD. **[Level C, Class IIa]**

Infections

Incidence

Infections are an important cause of morbidity and mortality post-transplant. Approximately 40% of paediatric patients suffer one or more infections during the first year post-transplant which represents 0.84 infections per patient.[212] This number is again higher (50%) in patients who are more ill at the time of listing, especially those less than 6 months of age. The risk of infection is 25 % at 1 month after transplantation, 42% at 6 months and 48% at 1 year. The overall risk of infection decreases with time after transplantation, and as in the adult population, is likely related to the decreasing risk of rejection over time and a decrease in immunosuppressive medications.[213]

Risk factors

Recognized risk factors for earlier onset of infections include younger recipient age, ventilator support at time of transplantation, positive donor Cytomegalovirus (CMV) serology with negative recipient serology and longer donor ischemic time.[212]

Type of infections

The majority of infections occur in patients less than 6 months of age at time of transplantation.[212] Bacterial infections are the most common type of infection, followed by viral, fungal and protozoal infections. The most common bacterial pathogens isolated include Staphylococcal species, Pseudomonas species, and Enterobacter species. Cytomegalovirus is one of the most common viral infections, followed by Varicella zoster, Respiratory syncytial virus and Herpes simplex virus. Candida species and Aspergillus species are the most common fungus isolated.

A number of infections are predictable based on experience and can be managed with standard prophylactic, pre-emptive or full treatment protocols. In order to facilitate this, both donors and recipients undergo extensive screening, both serologic and other, to predict potential donor organ-acquired infections that may require prophylactic or pre-emptive treatment in the highest risk time period (immediately post-transplant). Examples of this include the Epstein-Barr Virus (EBV), cytomegalovirus (CMV), and toxoplasma.

Certain pre-existing infections may become reactivated following introduction of immunosuppression. Again, pre-transplant serologic testing would identify the possibility to heighten awareness, and routine post-transplant surveillance can sometimes allow for prophylactic or pre-emptive treatment (EBV, CMV, Hepatitis B, Hepatitis C). Reactivation disease may also require treatment due to concurrent immunosuppression (i.e. varicella, shingles).

Outcomes

Most infections after paediatric heart transplantation can be successfully treated, and mortality is significantly related to the type and site of infection. Overall, at one year post-

transplant, mortality related to infection is around 7%. The peak risk of death from infection occurs approximately 1 month after transplantation. CMV infection is associated with only 5% mortality and the mortality of bacterial infection is about 15%, but mortality of fungal infections exceeds 50%.

Epstein Barr Virus (EBV)

The American Society of Transplantation (AST) recently published a review of EBV in relation to solid organ transplantation.[214] EBV-associated disease is of particular concern in the paediatric population due to the often lack of exposure to EBV prior to transplantation and the immunosuppressive state. Primary EBV infection occurring after transplantation is the most clearly identified risk factor for the development of post-transplant lymphoproliferative disorder (see PTLD below). Therefore, a significant proportion of transplant programs do advocate preventative therapy as the optimal strategy for management in the form of either chemoprophylaxis and/or preemptive strategies, using EBV viral load surveillance. However, prospective controlled data to support this is lacking.

In general, EBV serostatus should be determined for all patients at the time of listing and transplantation. Chemoprophylaxis should be considered as per the AST recommendations. This would consist of anti-viral therapy (ganciclovir or acyclovir) and/or passive administration of neutralizing antibodies through intravenous immune globulin. Choice of route (oral or intravenous), choice of drug (acyclovir or ganciclovir), and duration of therapy varies highly from centre to centre. Pre-emptive therapy in light of newer modalities for monitoring viral load is promising, but not currently recommended for routine use.

Cytomegalovirus (CMV)

Both the AST and Canadian Society of Transplantation (CST) have recently published consensus recommendations for CMV management in solid organ transplantation.[215,216] In general, for donor positive, recipient negative combinations, recommendations include prophylaxis for 1-3 months with an anti-viral agent with some centres adding CMV immune globulin for high-risk patients. For recipient positive patients, similar prophylaxis may be used, or a preemptive strategy utilizing CMV antigenemia testing with anti-viral therapy initiation at the time of conversion. Specific mention is made of the issues pertinent to paediatrics including the lack of data on the appropriate dose and efficacy of oral ganciclovir and oral valganciclovir in children with a comment that CMV chemoprophylaxis is based on the use of IV ganciclovir, and comments on the factors that influence the duration of prophylaxis which range from 14 days to 3 months.[216]

Toxoplasma

Toxoplasma may be transmitted from the donor to the recipient. In the case of a seropositive donor and a seronegative recipient, there are two possible approaches: prophylactic or pre-emptive therapy.[217] Prophylactic therapy should be commenced immediately post-transplant, consist of pyrimethamine and folinic acid, and be continued for a total of 6 months. Preemptive therapy should be started at the time of seroconversion, continued for 6 weeks, and should consist of pyrimethamine, folinic acid, and sulfadiazine.

Pneumocystis carinii

All patients should be considered at risk and consideration should be given to prophylaxis for the first year post-transplantation with trimethoprim/sulphamethoxazole. For patients with sensitivities to sulpha drugs, consideration should be given to use of either dapsone or monthly

pentamidine (aerosolized or intravenous). After one year post-transplant, prophylaxis may be discontinued unless indicated for another reason.

Candidiasis

Oral candidiasis and candidiasis of the diaper area in infants is very common post-transplantation. Consideration should be given to the use of Nystatin mouthwash prophylaxis administered three to four times daily in patients while on prednisone. If the patient is weaned from prednisone, the Nystatin is discontinued. However, if evidence of candidiasis should recur, treatment should be reinstituted. For difficult to treat cases of oral candidiasis in infants and toddlers, consideration should be given to a short course of gentian violet treatment.

Endocarditis

All patients are at risk of bacterial endocarditis following heart transplantation and prophylaxis should be given according to standard guidelines.[218]

Varicella zoster virus

All paediatric patients should be screened pre-transplant for antibodies to varicella zoster virus. If timing allows and they are seronegative, then patients should be immunized pre-transplant. If patients are seronegative, then they are at risk post-transplant of primary varicella infection. Any exposure (defined as greater than or equal to 20 minutes in the same room with a patient 48 hours prior to clinical development of varicella rash and while the rash remains vesicular) should be managed with administration of varicella zoster immune globulin (within 96 hours of exposure). All paediatric transplant recipients who develop acute varicella zoster should be admitted to hospital for intravenous antiviral therapy (acyclovir) until the last new lesions crust over because of the risk of disseminated varicella infection.

Common infections and their management

Transplant patients are susceptible to common viral upper respiratory tract infections that do not require antibiotic therapy. Gastroenteritis with vomiting and diarrhea is another common childhood illness that is prevalent in the paediatric population and can be managed with supportive therapies (i.e. oral rehydration). An added challenge in this patient population is the administration of and variation in the absorption of immunosuppressant drugs with an acute illness. In general, however, these common childhood illnesses are tolerated well on an outpatient basis and do not require specific therapy. There must, however, be a high index of suspicion for uncommon pathogens and efforts should be made to ascertain a specific diagnosis, especially in an unexpectedly prolonged or clinically severe situation. This should include appropriate sampling for viral, bacterial, fungal and protozoal organisms with the guidance of an experienced paediatric transplant physician or infectious disease specialist. An approach to pneumonia/pneumonitis and central nervous system infections in the post-transplant patient population is outlined in the adult consensus guidelines.[1]

Immunizations

Many paediatric transplant recipients will not have finished their routine schedule of immunizations prior to transplantation. Antibody titres should be checked pre-transplant. Efforts should be made pre-transplant to immunize with as many vaccinations as is feasible and developmentally appropriate, most importantly live viral vaccines. Post-transplant, vaccination schedules should not be resumed for 6 months, but may then follow appropriate schedules (see Table 4). ***Patients should never receive live viral vaccines post-transplant*** regardless of the fact that they are in the routine immunization schedule. Appropriate titres should be checked post-vaccination to determine response given the suppression of the immune system. In the case of

negative titres, consideration should be given to a repeat vaccination course under the guidance of an experience paediatric heart transplant physician or infectious disease specialist.

Table 4: Hospital For Sick Children Heart Transplant Program Immunization Schedule: Pre- and Post-Heart Transplant*

Based on Health Canada's National Advisory Committee on Immunizations recommended immunization schedule for infants, children and youth (Update 2004)
Revised 05/01/11

Immunization	**Pre Transplant**	**Post Transplant**	**Notes**
DTaP/IPV/HIB	2 months of age 4 months of age 6 months of age 18 months of age	Start >6 months post Tx • Initial visit • 2 months after 1st • 2 months after 2nd • 12 months after 3rd	**Do <u>not</u> give <u>oral</u> polio post-transplant** Do follow up titres
DTaP/IPV Booster	4-6 years of age	2 years of age* 4-6 years of age	* give if immunizations <u>started</u> post-transplant
dTap or Td Booster	14-16 years of age	14-16 years of age	
MMR **Pre-transplant only**	After 1st birthday (minimum age 4- 6 months if being listed)	DO NOT GIVE POST-TRANSPLANT	Do follow up titres
MMR Booster **Pre- transplant only**	18 months		
Hep B	Infancy or preadolescence (3 doses) If previously immunized, check titres and give booster dose if necessary preTx.	If no protective antibodies, need series of 3 doses starting at least 6 months post-transplant Post-Tx dose is **40 μg** (no minimum age or weight)	Do follow up titres
Varicella Pre-transplant only	After 1st birthday (minimum age 9 months if being listed)	DO NOT GIVE POST-TRANSPLANT	
VZIG		Give within 96 hours of appropriate exposure	
Pneumococcal conjugate (*Prevnar*)	**Infants** 2 months of age 4 months of age 6 months of age 15 months of age <u>7-11 months of age</u>	Start >4 months post Tx • Initial dose • 2 months after 1st • 2 months after 2nd	Posttx protocol is currently a study protocol at HSC and remains the recommended protocol postTx pending further clinical follow up

Pneumococcal polysaccharide (23-valent vaccine, eg. *Pneumovax*)	2 doses, 2 months apart 15 months <u>12-23 months of age</u> 2 doses, 2 months apart **Older than 24 months** One dose	4-6 weeks after conjugate vaccine as a booster	
Meningococcal C conjugate (eg. *Menjugate*) Can consider any of the meningococcal C conjugate vaccines Quadrivalent meningococcal vaccine (eg. *Menomune*, ACYW135)	**Infants** **12 months of age** **Older than 12 months** 1 dose in early childhood or at age 12 y	Start >4 months post Tx <u>4-11 months of age</u> 2 doses 4 weeks apart <u>12-24 months of age</u> 1 dose followed by quadrivalent vaccine at 24 months of age >24 months of age 1 dose followed by quadrivalent vaccine in 4-6 weeks See above	
Influenza (inactived)		Annually every fall Minimum age 6 months (4 months of age if transplanted during/immediately prior to flu season)	The live vaccine in the US is contraindicated
RSV monoclonal antibody (*Synagis*)	As appropriate for underlying disease (see CPS guidelines)	New Tx: <5 yrs of age Tx during the RSV season (Nov - Mar) or Tx within 3 months prior to the start of the RSV season (may substitute RSV-IVIG if patient being treated with CMV Ig) Older Tx: <5 yrs of age with risk factor (i.e. chronic lung disease)	
Hep A		May be given as part of combined vaccine with Hep B High risk patients (i.e. travel)	

Malignancy

Malignancies are another important cause of morbidity and mortality post-transplantation. They can occur de novo as reactivation of previous cancer, or due to chronic viral infections. The latter is the most significant in the paediatric population, however, the incidence of malignancy in the paediatric population is much less than in the adult population, with freedom from malignancy for the first 5 years post-transplant reaching over 95%.[3] From the PHTS database, there were 49 malignancies in 1,114 patients (0.04%), with 39 (93%) being due to post-transplant lymphoproliferative disorder (PTLD).[4] Survival with PTLD was 95% at 1 month, 67% at 1 year, and 63% at 5 years. Again, as with any registries, these numbers depend on reporting and underestimate the estimates from other sources.

Post-transplant lymphoproliferative disorder

As noted above, there is a recent excellent review of EBV and lymphoproliferative disorders in relation to solid organ transplant recipients with recommendations for diagnosis, investigation, prevention, treatment and surveillance recently endorsed by AST.[214] Post-transplant lymphoproliferative disorder (PTLD) refers to all clinical syndromes associated with lymphoproliferation post-transplant ranging from a mononucleosis-like illness to malignancies with clonal abnormalities.[219] EBV plays a major role in the development of PTLD with the highest risk for development being a primary EBV infection, though not all PTLD is EBV-related.[220] As noted above, given the naivety of the paediatric population to EBV, primary infection and, consequently, PTLD is more common in paediatric patients. Patients should be diagnosed and managed under the combined care of the paediatric heart transplant specialist, an infectious disease specialist and an oncologist with experience in dealing with PTLD.

The clinical presentation of PTLD is variable and may include a) asymptomatic localized adenopathy, tonsillar hypertrophy or lymphoid masses, b) oral ulcers or specific organ-related syndromes including a pneumonitic process, diarrhea or malabsorption syndromes, neurologic complaints, hematologic abnormalities, or c) nonspecific constitutional complaints including fever, lethargy, and failure to thrive. The diagnosis must be made based on a high index of suspicion, patient risk factors, rising EBV load and ultimately, a tissue sample for histologic identification and typing. Staging should consist of computed tomography (CT) scanning of the head, neck, chest, abdomen and pelvis, bone marrow aspiration, and lumbar puncture.

There are no controlled clinical trials comparing interventions or therapies for PTLD. The most important initial treatment is to reduce immunosuppression (or even discontinue). Anti-viral medication in combination with immunoglobulin therapy is the mainstay of treatment with both acyclovir and ganciclovir having beneficial effects.[221,222] There are newer modified chemotherapeutic regimens including monoclonal antibodies (i.e. rituximab) that are showing promise.[223,224] Adjunctive therapy has included conventional chemotherapy, tumour debulking and local radiation.

Patients who have recovered from PTLD or are at risk for PTLD are often on a regular surveillance protocol that can vary from centre to centre. This can range from standard physical examinations and EBV PCR testing at a predetermined routine interval (i.e. every 3-4 months), to regular radiologic imaging for asymptomatic disease or disease recurrence by CT scanning. Because of the concern of the amount of radiation exposure attributable to repetitive CT scanning, an alternative screening strategy for the recovered or at risk patient is follow up interval chest radiographs and abdominal ultrasounds.

12. Recommendations: PTLD

1. All paediatric patients should be screened routinely for the development of PTLD. The screening utilized should parallel their individual risk factors. **[Level C]**
2. PTLD should be diagnosed and managed under the combined care of the paediatric heart transplant specialist, an infectious disease specialist and an oncologist with experience in dealing with PTLD. **[Level C]**
3. Treatment options include lowering of immunosuppressive therapy, administration of anti-viral agents, immunoglobulin therapy, chemotherapeutic regimens that include the newer monoclonal antibodies (i.e. rituximab). Adjunctive therapy may include conventional chemotherapy, surgical debulking or radiation when necessary. **[Level C]**

Other Complications

Renal dysfunction

Renal dysfunction can be a significant source of morbidity in the post-transplant period.[225,226] There may be antecedent compromise due to low cardiac output, chronic diuretic therapy, or mechanical support. Post-transplant, there are further insults perioperatively due to hemodynamic instability and multiple nephrotoxic agents. Patients should undergo annual renal function testing including a measured or calculated glomerular filtration rate and screening for renal tubular acidosis. Hypertension should be aggressively screened for and treated. Strategies to prevent progressive renal dysfunction should be considered including minimizing calcineurin inhibitors with kidney-sparing IS (i.e. MMF, sirolimus). Rarely, dialysis or even renal transplantation is required.

Osteopenia/osteoporosis

Osteopenia can be medically significant if it leads to osteoporosis and subsequent pathologic fractures.[227] Many of the older patients with congenital heart disease have pre-existing osteopenia due to lack of mobility or exercise. Post-transplant, the risk of osteopenia is contributed to by steroids and calcineurin inhibitors. Screening should be done with an annual assessment of bone mineral density and prophylaxis or treatment as appropriate. Treatment alternatives include calcium and vitamin D supplementation, calcitriol, oral bisphosphonate therapy, and, for the most severe cases, intravenous bisphosphonates.

Growth

Growth retardation is a well-recognized morbidity in paediatric heart transplant recipients. Amongst the population followed by PHTS, growth velocity fell between the time of listing and the time of transplant. Catch-up linear growth occurred during the first year, but patients remained shorter than their age-matched peers at 6 years post-transplant. Patients transplanted for reasons other then congenital heart disease maintained steady linear growth post-transplant, but also did not achieve population means. Patients with a diagnosis of HLHS or those at a younger age at transplant showed less catch up growth.[228]

Growth data has also been analyzed in relation to steroid use post-transplant.[3] Though there were some minor differences with regards to height (linear growth) off prednisone, there did not appear to be any differences in weight gain across the age groups. Therefore, linear growth may be improved by using steroid-minimizing or steroid-sparing protocols.

Adherence

There is significant mortality and morbidity related to non-adherence in adolescent and young adult transplant recipients, with a high risk of non-adherence and graft loss in the first 2-3

years after transfer to an adult program.[229] Teens who have good socialization and communication skills, who feel empowered, and feel that they have some control over the situation are more likely to be adherent after a transplant.[230] Non-adherence is more likely in teens with a psychiatric disorder[231], a history of substance abuse[232], a history of physical or sexual abuse[232], or a belief that chance controls their health outcomes.[233] Family chaos, financial issues, an overly relaxed approach to parenting, few opportunities for teen autonomy, and family beliefs that things other than health are to be highly valued are all family issues that have an impact on adherence. Fear is a poor motivating factor.

Interventions can be focused in six areas: education, the relationship between the health care provider and the teen, medication, family, peers and psychiatric issues. Educational programs should be aimed both at increasing knowledge and developing skills. It should include regular updates about transplant and medication from a member of the team. A yearly "transplant day" can incorporate didactic and hands-on learning, with time for social activities, which will increase the chance of teens coming and will help those who are feeling isolated. Information should be presented in multiple formats —verbal, written, videos or computer based. The teen should be seen alone for at least part of every visit and are more likely to be adherent if they feel they are treated with respect and seen as individuals. Their concerns should be addressed. The teen will feel more "ownership" in their treatment if they are involved in the decision making.

As much as possible, medication regimens should be individualized. Medications that are taken only once or twice a day result in dramatic increases in adherence as compared to those taken three or four times a day.[234] As many medications as possible should be given together, and try for times when there is a routine cue to remind them (like brushing their teeth at bed time.) Consider the formulation, including size of pills and taste. Discuss side effects and ways

to minimize them. Self monitoring with a chart, calendar or PDA can provide motivation, visual feedback and a way for the team to see when and how often the teen is taking their medication.

Re-transplantation

A major concern in paediatric heart transplantation is the expected duration of graft survival. The 50% survival post-paediatric and adult heart transplantation is approximately 11 years (not including infant recipients).[3] The implication of this is that paediatric patients who survive the initial transplant period will likely require re-transplantation in order to survive into adulthood.

Re-transplantation should be considered in a failing graft. The most common causes for this include severe rejection and TCAD. According to ISHLT, the percent of patients with re-transplantation as the indication for heart transplant has risen to 7% since 1996.[3] Concerns about re-transplantation include the re-exposure of patients to medications used for immunosuppression. According to ISHLT data, approximately 40% of paediatric transplants performed internationally use induction therapy, most commonly polyclonal cytolytic therapy (see above).[3] The cumulative use of these immunosuppressive medications over time can result in a higher risk of complications from these agents such as hypertension, renal failure, diabetes and malignancy – serious concerns in retransplantation.

According to the ISHLT data from 2002, in adult heart transplantation, the risk of 1 year mortality is increased 1.5-fold in patients undergoing re-transplantation. The risk of 5 year mortality is increased more than 2-fold in patients who have had a previous transplant. Paediatric data from the same source suggests that the 1 year mortality is NOT affected by re-transplantation but the 5 year mortality is increased 3.4 fold. Razzouk and colleagues reported a

similar operative mortality (8.3% vs. 9.0%, p=0.9) and late survival (83.3% vs. 74.4% at 4 years, p=0.85) for children undergoing re-transplantation for TCAD compared to paediatric patients undergoing primary cardiac transplantations.[202] Patients needing retransplantation within 6 months of their initial transplantation or those requiring a mechanical assist device remain poor candidates for re-transplantation.[235]

In general, select paediatric patients with graft failure and no absolute contraindications should be offered the option of retransplantation. However, ethical concerns remain regarding re-transplantation given the overall shortage of organ donors.

Pregnancy after heart transplantation

Successful pregnancies are possible after all types of solid organ transplantation and concerns in transplant recipients are mainly centered around maternal survival, graft function and effects of immunosuppresive drugs on the offspring. The outcome of pregnancy after kidney and liver transplantation has been extensively reported but cases of pregnancy after heart transplantation have been more sporadic. The largest retrospective multicenter study in women who have undergone heart transplantation reports the outcome of 47 pregnancies in 35 women that produce 35 live births (74%), 6 miscarriages and 6 abortions.[236] Fetal complications included a high incidence of prematurity (43%) and low birth weight (mean 2543 g). No structural malformations were identified in the newborn. The main maternal complication was hypertension with a higher risk of preeclampsia (20%-25%) compared to that reported in the general population (5%). Rejection rates during and after pregnancy did not exceed preconception rates.

All immunosuppressive drugs cross the placenta and have theoretical risks to the fetus.[237] Prednisone is part of virtually all immunosuppressive regimens. It can potentially increase the risk of premature rupture of membranes but has a low teratogenic risk. Ideally, azathioprine should be avoided because of evidence of thymic atrophy, leukopenia, anemia, thrombocytopenia, chromosome aberrations, reduced immunoglobulin levels with infections in the newborn as well as pre-term delivery and intrauterine growth retardation. Cyclosporine and tacrolimus are associated with a minimal teratogenic risk, a moderate risk of fetal growth retardation and premature delivery. However, their concentration must be closely monitored because the physiologic changes induced by pregnancy modify their bioavailability. MMF, which has now to a large extent replaced azathioprine, is teratogenic in animals. Data are lacking in humans but an increased risk could be present. No clinical pregnancy outcome data are available on sirolimus but in animals, it was associated with an increased fetal mortality when used with cyclosporine. No immunosuppressive regimen has been proven superior to another during pregnancy and risk of graft rejection must always be weighed against potential teratogenicity and fetal complications.

Ovarian function is often altered during the pre-transplantation period and transplantation generally restores fertility for unclear reasons. Transplanted women must therefore be informed about their restored fertility and contraception should be advised. Oral contraceptives are very effective in low-dose formulations. They are safe with few side-effects. However, the long-term impact of hormonal contraception in heart transplant recipients has not yet been well-documented.[238] Intrauterine devices (IUD) should be avoided as the risks of infection are greater in immunosuppressed female. When a heart transplanted recipient expresses a desire for pregnancy, she must be informed about the maternal and fetal risks. The pregnancy must be

planned and a 2-year period between transplantation and pregnancy is recommended to ensure good maternal general health, no evidence of rejection, no significant hypertension and clinical stability on the lowest dosage of immunosuppressive drugs. Because of the risk of premature birth and pre-eclampsia, high-risk obstetric support with the collaboration of a multidisciplinary team should be used for all heart transplant recipients.

MECHANICAL CIRCULATORY SUPPORT IN THE PAEDIATRIC POPULATION

The indications for mechanical circulatory support in the paediatric population include failure to wean from cardiopulmonary bypass post-repair of congenital heart defects, cardiogenic shock associated with acute or fulminant myocarditis, and end-stage congestive heart failure associated with cardiomyopathy. The primary objectives for this form of therapy are to support the circulation until there is sufficient myocardial recovery to allow separation from the device (bridge-to-recovery), and to stabilize patients in need of a heart transplant until a suitable donor is identified (bridge-to-transplant).

Technological advances in paediatric cardiac care assist have been limited by the anatomical and physiological constraints imposed by this patient population. Afterload reduction and diastolic augmentation are limited by a small, compliant aorta, rendering intra-aortic balloon counter-pulsation less effective in paediatric patients. Pulsatile ventricular assist devices (VADs) currently approved for clinical use in North America have been engineered according to the demands of average-sized adult patients, and there are none routinely available for implantation in small children. Extracorporeal membrane oxygenation (ECMO), and the Bio-Medicus centrifugal pump are easily adaptable for use in paediatric patients.

Indications

The most common indications for mechanical circulatory support in paediatric patients are intractable low cardiac output despite maximal pharmacologic therapy in patients with postcardiotomy cardiac failure, cardiomyopathy, or acute or fulminant myocarditis. The most frequent objective is to support the circulation while allowing the native myocardium to recover sufficient function to sustain life. The decision for cardiac replacement (transplantation) should be based on the potential for reversibility of the original pathologic process.

Recovery rates for patients with acute myocarditis requiring some form of mechanical circulatory support range from 20% to 66%. Most of this variation is due to differing thresholds for institution of mechanical support, and in definition of recovery. Only one- half of those who recover actually regain near-normal cardiac function, while the remainder remain compromised to a significant degree. Generally, greater benefit is achieved with early unloading of the heart with institution of mechanical support in patients who do not show a prompt improvement with pharmacological therapy.

Extracorporeal Membrane Oxygenation (ECMO)

An extracorporeal membrane oxygenation (ECMO) circuit consists of venous drainage and arterial inflow cannulas, a centrifugal pump, an oxygenator, and a heat exchanger. A dialysis membrane may be interposed within the circuit. Despite widespread use of heparin-bonded circuits, systemic anticoagulation is necessary, maintaining activated clotting times of 220-260 seconds. This requirement for anticoagulation frequently leads to bleeding complications, especially in patients being supported for post-cardiotomy cardiac failure. Additional significant

potential complications include hemolysis, platelet consumption, infection, clotting within the circuit, and oxygenator failure. Patients on ECMO support are confined to a critical bed, and frequently require sedation in order to minimize bleeding associated with movement. A major advantage of ECMO is its adaptability to patients of all sizes. Standard central cannulation using conventional cardiopulmonary bypass cannulas can be used, facilitating conversion to ECMO in post-cardiotomy cases.

The use of extracorporeal membrane oxygenation itself as a bridge to transplantation remains controversial given the high morbidity and mortality. Recovery rates in patients supported with ECMO range from 35% to 70%, with the worst outcomes seen in patients with incomplete repairs of cardiac defects. Results in patients requiring support for over 7 days are also poor. However, recent published reports support reasonable and acceptable outcomes.[239,240] Looking specifically at institutional results at the Hospital for Sick Children in Toronto, in patients supported by extracorporeal membrane oxygenation (ECMO), there were 18 patients who underwent heart transplantation from ECMO.[10] Median age was 6.8 years (10 days –17 years). Mean duration of ECMO was 5.7+3.8 days. Median follow up was 2.2 years (1 month – 7.2 years). Fourteen patients survived to hospital discharge. Univariate analysis of risk factors ($p<0.05$) for poor outcome were higher creatinine before and during ECMO, significant fungal infection, and high exposure to blood products. The following did not play a role in survival to hospital discharge: original diagnosis, duration of ECMO support, wait time from listing to transplant, lactate level, cardiac arrest, indication for ECMO, site of vascular cannulation, use of ultrafiltration or bacterial infection. Patients on ECMO support may have successful outcomes despite circumstances that may previously have been considered relative contraindications (cardiac arrest, length of support, bacterial infections).

Paracorporeal Ventricular Assist Devices

Pulsatile ventricular assist devices (VAD) are an established form of therapy as bridges to heart transplantation as well as support devices in post-cardiotomy cardiogenic shock. The Thoratec VAD and the Berlin Heart have short, valved inflow and outflow cannulas which traverse the chest wall and connect to blood pumps which sit externally on the abdominal wall (paracorporeal). The pumps are pneumatically-driven by external consoles. These devices can be used for uni- as well as bi-ventricular support, with the Berlin Heart being available in several sizes. Systemic anticoagulation is necessary. With the advent of small, portable consoles, all but the youngest patients can ambulate safely with these devices. Indeed, the goal in most such bridge-to-transplant cases should be to discharge patients safely from critical care settings, and some may leave hospital altogether to await a suitable donor, enabling full rehabilitation on a well-functioning VAD. Not all institutions have access to these devices.

Intracorporeal Ventricular Assist Devices

The Novacor Left Ventricular Assist System and the HeartMate Left Ventricular Assist Device are pusher-plate blood pumps implantable within the abdominal cavity or within the layers of the abdominal wall. The valved inflow conduit originates at the left ventricular apex, and a valved outflow conduit connects to the ascending aorta. The pumps are controlled by small modules connected via a percutaneous driveline. Batteries provide up to eight hours of autonomy on a single charge. Systemic anticoagulation and anti-platelet agents are necessary with the Novacor LVAS. The HeartMate's unique beaded blood-contacting surface prevents thrombosis, and therefore no anticoagulation is necessary in most cases. These pumps are available in only one size, and are generally not suitable for patients less than 1.5 m^2 body surface area. Due to the

more complex implant procedure, these devices are less practical in post-cardiotomy cardiogenic shock, or in patients with multiorgan failure, bleeding diathesis, or at imminent risk of death. Most individuals on this form of support can be safely managed as outpatients. Not all institutions have access to these devices.

13. Recommendations: Mechanical Support

1. Specific guidelines for institution of mechanical circulatory support are not developed for the paediatric population. Institution of mechanical support should be guided by patient circumstance, available resources, and institutional expertise. **[Level C]**

CONCLUSIONS

Cardiac transplantation is an acceptable therapeutic option for the paediatric age group and for adult patients with congenital heart disease as outlined above. There is minimal evidence-based literature in these patient populations to guide recipient management with regards to immunosuppression and post-transplant morbidities, and efforts need to be made to support multi-centre trials to determine optimal treatment protocols, especially for the paediatric population. Donor availability remains a major limiting factor in organ transplantation at the present time. Efforts need to be made to increase organ donor awareness, identify potential donors, and aggressively manage marginal donors. Consideration needs to be given to a parallel listing strategy for paediatric patients and for adult patients with CHD that better reflects the clinical course of deterioration in this patient population. As donor availability is not ever likely

to meet the need of potential recipients, ongoing medical and surgical therapeutic alternatives to transplantation need to be aggressively pursued, in addition to other alternatives such as mechanical assist devices. Xenotransplantation and stem cell therapies remain potential alternatives for the future. Further therapeutic modalities under development promise to further change the clinical course of transplantation and clinical outcomes.

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