The international society of heart and lung transplantation guidelines for the care of heart transplant recipients

TASK FORCE 3: Long-term Care of Heart Transplant Recipients (Aug. 6, 2010)

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Topic 1: Minimization of Immunosuppression

The principal goal of immunosuppressive therapy in heart transplantation (HT) is to maintain a fine balance between minimizing the risk of allograft rejection and minimizing the long-term morbidity associated with the adverse effects of immunosuppressive drugs.

Strategies for Minimization of Immunosuppression

Corticosteroid Minimization

Because corticosteroid (CS) therapy is associated with glucose intolerance, dyslipidemia, hypertension, osteoporosis and infection, minimizing its use after HT is highly desirable, when safe. Patients at low risk of rejection, including those without circulating anti-human leukocyte antigen (HLA) antibodies, non-multiparous women, those without a history of rejection, and older HT recipients may be considered for rapid CS weaning and withdrawal. In HT, a higher number of HLA mismatches is predictive of adverse outcomes with CS weaning.[1] Therefore, the degree of immuno-incompatibility should be considered when individualizing CS treatment strategies.

Early withdrawal of prednisone during the first month of HT in recipients of cytolytic induction therapy has been successful in 49% to 70% of patients.[2-4] Because the majority of acute rejection episodes occur during the first 6 months after HT, CS withdrawal after this period can be achieved in up to 80% of cases, even without prior induction therapy.[5, 6] According to the most recent International Society of Heart and Lung Transplantation (ISHLT) Registry data, > 40% of HT recipients are successfully maintained off CSs at 5 years.[7] A standardized protocol for CS withdrawal, guided by serial endomyocardial biopsy (EMB), is typically employed.

More recently, randomization of low-risk HT recipients to either an anti-thymocyte globulin (ATG)-based CS-avoidance regimen or a long-term CS-based regimen without antibody induction[8] showed that the 2 groups had similar rejection rates with lower short-term morbidity in the CS-avoidance group. Further studies to demonstrate the long-term safety and benefits of CS avoidance should be carried out.

Calcineurin Inhibitor Minimization

The cumulative incidence of chronic renal failure in HT recipients is estimated to be ≥ 10% at 5 years[9] and has been chiefly attributed to long-term calcineurin inhibitor (CNI) use. In general, the highest doses of CNIs are used early post-HT when the risk of rejection is the greatest followed by gradual reduction of CNI exposure thereafter. A number of trials have addressed the feasibility of CNI reduction or elimination in HT.[10-21] The use of mycophenolate mofetil (MMF) rather than azathioprine (AZA) has permitted successful lowering of CNI exposure,[22] with lower rates of rejection, improved renal function, and increased CS weaning. In a prospective, multicenter study,[11] substitution of AZA with MMF before cyclosporine (CYA) dose reduction resulted in a significant decrease in serum creatinine (sCr) in the intervention arm compared to a modest increase in the control group. Reduction of CYA was also associated with a significant decrease in blood pressure. A number of smaller single-center studies have produced concordant results.[12, 13, 19]

Late CYA reduction in HT recipients without adjunctive therapy, however, appears not to be associated with renal function improvement.[18] The substitution of sirolimus (SRL) for AZA also seems to be of limited benefit in the setting of CNI minimization, because these agents (proliferation signal inhibitors [PSIs]) may exacerbate CNI nephrotoxicity.[20, 23, 24] The use of PSIs for the specific purpose of CNI minimization to reduce nephrotoxicity remains controversial.

Calcineurin Inhibitor Withdrawal

Late post-HT substitution of SRL for CNI[21] or for MMF and targeting lower CNI levels appears to be beneficial with respect to improvement in renal function and cardiac allograft vasculopathy (CAV)[25] without increasing rejection rates. Early withdrawal of CNI with PSI substitution, however, has been associated with unacceptably high rejection rates.[14, 16, 26, 27] In summary, while use of SRL without a CNI is not advisable early after HT, when the risk of rejection is highest and therapeutic immunosuppression with a CNI is of greatest importance, substitution of the CNI may be a viable option late after HT in stable patients, in whom a significant improvement in renal function can be expected.[14, 16, 26]

Calcineurin Inhibitor Monotherapy

Very few studies have investigated the safety and efficacy of CNI monotherapy in HT recipients. A small study suggested the feasibility of initially using tacrolimus (TAC) with prednisone, with 75% of patients being subsequently weaned off CSs with acceptable rejection and improved survival rates. A subsequent randomized trial without induction therapy and with early withdrawal of CSs revealed comparable rejection rates between triple regimen and monotherapy groups at 1 year but longer term results are needed to determine the impact of this strategy on mortality, rejection, renal function, CAV, and malignancy.[28, 29]

Monitoring

Trough or pre-dose CNI levels are most commonly used (see Task Force 2, Topic 2: Monitoring of Immunosuppressive Drug Levels), but there is some evidence that monitoring of CYA levels at 2 hours after dosing (C2) may be a better indicator of immunosuppression efficacy than trough levels and may be associated with lower CNI exposure without adverse outcome and improved renal function.[30-32] Exposure to MMF may be measured with trough mycophenolic acid (MPA) levels. However, the relationship between MPA levels and rejection remains unclear.[33]

Pre-HT panel reactive antibodies (PRAs) have been correlated with post-HT adverse outcomes in HT recipients.[34, 35] Detection of anti-HLA antibodies by flow-cytometry both pre- and post-HT is more predictive of rejection compared with the complement-dependent cytotoxicity assay[35] and provides a useful marker that can be serially assessed during minimization of immunosuppression. Quantitation of flow-PRAs is also now possible with measurement of mean fluorescence intensities, which may further help stratify risk of rejection in patients with circulating antibodies. The presence of post-HT donor-specific antibodies is also a marker for the subsequent development of CAV.[36] The usefulness of serial allo-antibodies measurement after HT in guiding immunosuppression weaning has not yet been tested in prospective studies.

Immunosuppression Minimization in Pediatric Heart Transplantation

Given the known effects of CSs on growth, early withdrawal, minimization, or avoidance has long been a prominent goal in pediatric immunosuppression protocols, especially in infants.[37-40] Current ISHLT pediatric data[41] shows that > 40% of pediatric patients are not on maintenance CSs at 1 year after HT and this percentage increases to nearly 60% at 5 years after HT.

As in adults, pediatric immunosuppression generally is achieved with a combination of a CNI and an anti-proliferative agent. However, for several years some centers[39] have employed CNI monotherapy successfully in low-risk patients such as infant HT recipients. MMF is increasingly being used in the pediatric population to allow for CS withdrawal and lower CNI levels.[41]

Because of differences in CYA absorption patterns in pediatric patients, use of C2 levels for dose minimization is problematic.[42] Marked individual variations in the pharmacokinetics of MMF have also been observed in children.[43] Shorter half-lives with more rapid metabolism have been observed in pediatric renal transplant patients taking SRL without concomitant CNI.[44] Thus, strategies aimed at immunosuppression minimization in children may require a greater reliance on therapeutic drug level monitoring for individualization of drug dosing than is needed in adult patients.

Recommendations for the Minimization of Immunosuppression[2, 6, 8, 11, 15, 17, 18, 20, 22, 23, 25, 29, 38, 44]:

Class I:

1. CS withdrawal can be successfully achieved 3 to 6 months after HT in many low-risk patients (those without circulating anti-HLA antibodies, non-multiparous women, those without a history of rejection, and older HT recipients).

   Level of Evidence: B.

2. Lower levels of CNIs in HT recipients should be sought when CNIs are used in conjunction with MMF (compared to AZA) because with this combination lower levels are safe and associated with lower rejection rates as well as improved renal function.

   Level of Evidence: B.

Class IIa:

1. A PSI may be substituted for CNI later than 6 months after HT to reduce CNI-related nephrotoxicity and CAV in low risk recipients.

   Level of Evidence: C.

Class IIb:

1. CNI monotherapy with early CS withdrawal may be considered in highly selected individuals. This strategy has been associated with acceptable short-term outcomes in HT recipients.

   Level of Evidence: B.

2. In pediatric HT recipients, minimization of immunosuppression by CS withdrawal is common practice and appears safe, with the majority of children being free of CS by 5 years after HT.

   Level of Evidence: C.

3. Due to variable pharmacokinetics in children, strategies for minimization of immunosuppression in the pediatric population may require a greater reliance on drug level monitoring than in adults.

   Level of Evidence: C.

4. The use of PSIs may be considered in pediatric HT recipients to reduce CAV and nephrotoxicity, but insufficient data is available on the effects of PSIs in children.

   Level of Evidence: C.

Class III:

1. In HT recipients, substitution of PSI for MMF for the specific purpose of lowering CNI exposure to reduce CNI-related nephrotoxicity is not recommended due to the interaction between CNI and PSI, which enhances CNI nephrotoxicity.

   Level of Evidence: C.

2. Substitution of a PSI for MMF earlier than 3 months after HT is not recommended due to a higher risk of rejection as well as delayed wound healing.

   Level of Evidence: B.

Topic 2: Management of Neurologic Complications After Heart Transplantation

Neurologic complications occur frequently after HT and produce significant morbidity that reduces the patient's quality of life.[45] These complications are self-limited and not a principal cause of death.[46] The most frequently encountered neurologic complications are cerebrovascular complications (including ischemic and hemorrhagic stroke), seizures, encephalopathy, central nervous system (CNS) infections, and peripheral neuropathies.[45-50] Headache, tremor, and insomnia are common in CNI-treated patients. In general, these side effects are dose related, and usually subside with dose reduction.

While the incidence of most neurologic complications is decreasing, the incidence of cerebrovascular events in the perioperative period has remained unchanged.[46, 50] The reported 9% incidence of focal ischemic neurologic complications exceeds the 1% to 5% incidence reported from patients undergoing conventional cardiac surgery. The increasing use of mechanical circulatory support (MCS) devices may account for some of this additional risk. Aspirin is frequently prescribed after HT, but its effect on cerebrovascular complications is unknown.

Seizures have been reported in about 15% of adult and 40% of pediatric patients, occurring most often peri-operatively as a result of focal ischemic injury, anoxic encephalopathy, CNI toxicity, or metabolic derangements.[49] Seizures occurring after the first month typically arise from CNI toxicity or from opportunistic CNS infection. Hypomagnesemia, hyponatremia, and hypertension may enhance the risk of seizures whereas CNI reduction or avoidance lowers the risk of subsequent seizures. Long-term anti-convulsant therapy is rarely indicated. When anti-convulsant therapy is necessary, it is important to know that certain anti-convulsants, such as carbamazepine, fosphenytoin, phenytoin, and phenobarbital increase the metabolism of CNIs, most likely through induction of hepatic cytochrome P-450 (CYP-450) enzymes. Serum levels of the CNIs should be monitored closely and doses adjusted when these medications are prescribed. The use of levetiracetam does not appear to affect CNI levels.

Encephalopathies occurring in the immediate post-operative period are usually multi-factorial, whereas those occurring later usually have a specific neurologic cause.[45, 49] Cyclosporine, and perhaps TAC, can produce posterior reversible encephalopathy syndrome (PRES).[51] This leukoencephalopathy presents with headache, visual changes, and seizures in the setting of hypoattenuated cortical and subcortical lesions with T2-weighted magnetic resonance brain imaging. Reduction or withdrawal of CNI (often with change to the alternative CNI) can reverse the syndrome in most cases, but under-immunosuppression should be carefully avoided.[51, 52]

The incidence of intracranial infection is declining due to greater acceptance of lower levels of immune suppression.[46, 53]

The causative organisms differ depending upon the time after HT, and knowledge of the potential pathogens based on this fact can improve outcomes.[49]

Disorders of the peripheral nervous system can occur early or late after HT.[54] Brachial plexopathy from patient positioning or peroneal nerve injury from intra-aortic balloon placement may occur peri-operatively. Sensory polyneuropathies are commonly reported in HT recipients with diabetes, renal failure, or amyloidosis. Gabapentin and tricyclic antidepressants are frequently prescribed, but outcome data are scarce. Neurologic complications in children and adults after HT are similar in both incidence and type, except that peripheral neuropathies are more commonly seen in adults.[49] Children also face a small additional risk of developmental delay.

Recommendations for the Management of Neurological Complications After Heart Transplantation[45, 46, 49, 54]:

Class I:

1. Management of HT recipients with seizures should include reduction of CNI doses (taking into consideration the risk of inadequate immunosuppression) and correction of hypomagnesemia, if present.

   Level of Evidence: C.

2. The occurrence of encephalopathy late after HT should prompt neurological consultation and imaging to identify possible underlying etiologies.

   Level of Evidence: C.

3. PRES in HT recipients should be managed with a reduction of CNI doses or substitution with an alternative CNI.

   Level of Evidence: C.

Class IIb:

1. HT recipients who continue to experience seizures after a reduction in CNI dose may benefit from CNI withdrawal and substitution with a PSI (SRL, everolimus [EVL]).

   Level of Evidence: C.

Topic 3: Cardiac Allograft Vasculopathy

The long-term survival of HT recipients continues to be limited in large part by the development of CAV. Major improvements in the prevention and treatment of rejection have not been paralleled by similar improvements in the incidence and mortality of CAV.[55] Symptoms of CAV usually appear when the disease is no longer amenable to therapeutic intervention. Surveillance is, therefore, required for early detection of CAV. In general, non-invasive methods cannot detect early disease as their positive findings occur in the presence of flow-limiting coronary lesions and sensitivity is limited by the diffuse nature of the disease.

Coronary angiography is the invasive method most commonly used screen for CAV. In addition to the annual evaluation, at some centers "baseline" angiography is performed early after HT to exclude donor coronary artery disease (CAD), particularly when older donors (> 35 years) had not undergone a pre-harvest angiography. Although the optimal schedule for angiographic screening has not been established, at most centers the procedure is performed annually or biannually.

The diffuse, concentric, and longitudinal nature of CAV often results in underestimation of disease by angiography because there is no normal reference segment to which the diameter of the vessel can be compared. Minimal luminal irregularities may suggest the presence of early disease. Comparison with prior studies may help identify the development of disease, but it requires the use of the same angiographic protocol at each study to avoid confounding by different angiographic projections and magnification. The use of computer-assisted quantitative coronary angiography (QCA) improves the sensitivity of the detection of CAV, but it does not allow evaluation of the vessel wall and may miss early disease where the luminar area of the vessel is preserved due to compensatory dilatation.

Selective coronary angiography is possible in children, who require general anesthesia for the procedure. Although catheters with small curves are available, the procedure is technically difficult in infants. Because spasm of the coronary arteries, particularly the right, is common in children, coronary artery stenosis can be diagnosed only after the intracoronary injection of nitroglycerin has excluded coronary spasm. Occasionally selective angiography is impossible and visualization of the coronary arteries may be achieved via injections into the aortic root. Care should be taken not to damage the femoral artery by using small French gauge sheaths, the volume of contrast should be limited to avoid nephrotoxicity and X-ray exposure kept to a minimum.

Intravascular ultrasound (IVUS) performed at the time of coronary angiography allows direct imaging of the vessel wall. This has been useful in identifying donor-related CAD in the early post-operative period and in the serial evaluation of coronary arteries lesions acquired after HT.[56-60] Importantly, the finding of intimal thickening ≥ 0.5 mm in the first year after HT is a reliable surrogate marker for subsequent mortality, non-fatal major adverse cardiac events, and

development of angiographic CAV through 5 years after HT in adults.[61] However IVUS has several limitations—it is highly invasive, requires anticoagulation, use of expensive single-use catheters, and evaluation is mainly limited to the major epicardial vessels. Basic criteria for interpreting IVUS measurements are in Table 1.

Table 1 Basic Criteria for the Interpretation of Intravascular Ultrasound Measurements After Heart Transplantation

Normal		Abnormal
Baseline study (4-6 weeks post transplant)	0.25-0.5mm intimal thickness	Any intimal lesion ≥ 0.5 mm suggests donor disease[56]
1-year study	No change in intimal thickness expected	Any lesion change from baseline - > 0.5-mm change suggests accelerated disease associated with adverse outcomes[61]

According to several reports coronary artery IVUS is safe in children,[62, 63] although it is technically more challenging in small children and not feasible in infants. Therefore, IVUS is more widely used in the second decade. In contrast to the adult population, in which the prognostic value of serial changes IVUS measurements is well established, the limited evidence in children has largely been obtained from cross-sectional analyses.

The frequency of angiography and IVUS can be decreased in patients free of CAV at 5 years, especially if the patients have renal insufficiency. If percutaneous coronary intervention (PCI) is done for CAV, repeat angiography may be performed after 6 months due to the higher restenosis rates seen in transplant recipients at least in those not receiving stents.[64]

Endothelial dysfunction occurring with CAV can be uncovered by the finding of an abnormal coronary flow reserve (CFR) and impaired endothelium-dependent relazation. Intracoronary flow velocities are determined using a Doppler transducer mounted on a guide wire and changes in coronary blood flow in response to endothelium dependent and independent vasodilators can be assessed. With CAV, CFR drops with increasing time after HT.[65, 66] Measurement of CFR is particularly useful in assessing microvascular abnormalities. In HT recipients with angiographically normal coronaries, impaired CFR is correlated with IVUS-derived plaque volume and it predicts deterioration of left ventricular (LV) function 2 years later.[67] The prognostic value of CFR measurements in HT recipients has not been tested in controlled clinical trials.[68]As in adults CFR measurement in children correlates with CAV,[66] but its value in predicting CAV progression and prognosis is unknown.

Ultrafast computerized tomography (CT), used to detect coronary calcification, may be useful in the detection of CAV,[69] recognizing its inability to provide detailed information on the vessel wall and lumen. Coronary calcification has been shown to correlate with angiographic disease, CAD risk factors including hypertension, dyslipidemia, and hypertension and with clinical outcomes.[70, 71] Although the high heart rates and obesity frequently present in HT recipients makes CT angiography challenging in this population, it has high specificity and negative predictive value (NPV) for detection of CAV[72, 73] and may, therefore, have a potential role in screening for the disease.

Dobutamine stress echocardiography (DSE) has been successfully used for CAV screening and may be particularly useful in the pediatric population, with a high correlation between an abnormal DSE and angiographically detectable CAV.[74] Quantitative enhancements using myocardial echo-contrast or tissue Doppler imaging may further improve the sensitivity and specificity of DSE in the evaluation of CAV.[75, 76]

In 1 study, absence of reversible defects by myocardial perfusion imaging virtually excluded lesions severe enough to require coronary artery revascularization.[77] After HT perfusion abnormalities may also independently predict cardiac death.[78]

The need for general anesthesia and the technical difficulties of coronary angiography in the young makes non-invasive testing for CAV in children attractive. In children, myocardial perfusion imaging and stress echocardiography may not detect all CAV.[79] Although abnormalities detected by DSE appear to correlate with angiographic evidence of CAV,[74] DSE can distress some children. Longer term data on the prognostic value of these tests is needed before they can replace invasive testing in the pediatric population.

Risk Factor Modification

Prevention is the best approach for CAV and must be initiated early because most of the intimal thickening occurs during the first year after HT. Preventive measures include avoidance of endothelial damage during donor organ harvest and implantation, reduction of acute rejection, prophylaxis for cytomegalovirus (CMV) infection, and aggressive therapy for traditional risk factors for vascular disease.[80-82]

Resumption of smoking after HT in adults is associated with death from CAV and malignancy,[83, 84] so smoking cessation is extremely important. Smoking is a problem in

adolescents and, although there is no evidence that smoking is a risk factor for pediatric CAV, it is plausible that it may be associated with risk comparable to that in adults.

Although in adults obesity has been correlated to poor graft and patient survival, evidence of a direct association with the development of CAV is lacking.[85, 86] However, given that obesity is common in HT recipients due to effect of CSs and that it is likely to contribute to CAV risk factors (diabetes, hypertension, and hyperlipidemia), an aggressive approach to weight control is recommended. Obesity is less common in children than in adults, and there are no data linking body-mass index (BMI) to CAV or mortality.[87] CMV infection is another recognized risk factor for the development of CAV.[88, 89] Although CMV immunoglobulin, ganciclovir, or valganciclovir are commonly used for the prevention of infection, the effects of prophylaxis on altering the course of CAV remain unclear. CMV also appears to be a risk factor for CAV in children.[90, 91] No conclusive evidence exists in children on whether prophylaxis or pre-emptive treatments for CMV reduce the risk of CAV.

Diabetes is common in adult HT patients (and is discussed in more detail in Topic 6), with 1-year rates up to 30%.[55] The risk factors for new-onset diabetes include pre-operative glucose intolerance, a family history of diabetes,[92] elevated pre-transplant BMI,[93] the need for insulin on the second day after HT, and immunosuppressive drugs,[92] particularly CNIs and CSs.[94] Compared to CYA, TAC is also associated with a higher incidence of diabetes.[95, 96] Glycosylated hemoglobin (HbA1c) has been correlated with the severity of CAV detected either by angiography or IVUS.[97] Therefore, an aggressive approach to glycemic control after HT is an important component of CAV prevention. Despite widespread use of TAC in children, diabetes is uncommon and hypertension less frequent than in adults. This may be related to CS avoidance in many pediatric programs.

A retrospective analysis suggests a correlation between hypertension and CAV.[98] There is evidence that the use of calcium channel blockers may attenuate the development of CAV. In 1 study,[99] treatment with diltiazem was associated with significantly less reduction in angiographic coronary artery luminal diameter at 1 and 5 years and lower CAV and death rates at 5 years. Importantly, this non-randomized study was done before routine use of statin therapy and availability of IVUS measurements. Angiotensin converting enzyme inhibitors (ACEI) may act synergistically with calcium channel blockers in attenuating CAV as determined by IVUS.[100] (See section on statins in Task Force 2.)

Alternative Immunosuppressive Strategies

There is no evidence of that CYA- and TAC-based therapies are associated with different CAV rates. The finding that, compared to AZA, MMF used in combination with CYA and CSs was associated with reduced progression of intimal thickening at 1 year after HT,[101] has contributed to widespread substitution of AZA with MMF. The most promising drugs for reduction of CAV are the PSIs (mammalian target of rapamycin [mTOR] inhibitors). Use of PSIs (EVL and SRL) has been shown to significantly reduce the intimal thickening of allograft coronary arteries compared to AZA and to be associated with reduction of CAV at 12 and at 24 months.[102-105] The side effects of PSIs[106] and lack of additional survival[103, 104, 107] are major factors limiting their use. In children, there are no data on the ability of PSIs to reduce the incidence or severity of CAV.

Treatment of Established Cardiac Allograft Vasculopathy

Pharmacologic treatment options for established CAV are limited. Preliminary data showed promising results with SRL,[25, 108] but these have not been confirmed by a controlled clinical trial.

For focal disease, PCI such as balloon angioplasty have been successful, but restenosis was common in the HT setting before the use of stents.[109, 110] The availability of drug-eluting stents has decreased CAV restenosis rates,[64] but the need for repeat interventions remains high,[111] primarily due to the development of de novo lesions. Although drug-eluting stents have lower restenosis rates than bare-metal stents,[112] survival is similar with the 2 types of stents and 1-year mortality after PCI is 32%.[113] Because it is unknown whether PCI alters the prognosis of CAV and many patients with significant disease are asymptomatic, it is often difficult to decide whether to proceed with PCI. Coronary artery bypass grafting can be performed in highly selected patients[114] because the diffuse nature of the CAV prevents the use of surgical revascularization in most HT recipients.

The only definitive therapy for CAV is retransplantation and that may be considered for highly selected patients with advanced CAV not amenable to PCI and associated with allograft dysfunction. Although overall survival after retransplantation is lower than for primary transplantation,[115] retransplantation specifically for CAV has been associated with comparable outcomes to those after primary transplant.[116-118] This issue is discussed in more detail in Topic 17.

Recommendations for the Diagnosis and Management of Cardiac Allograft Vasculopathy[56, 58, 61-63, 69, 73-76, 81, 84, 88, 90, 91, 97, 99-103, 108, 110, 112, 117]

(See Table 1)

Class I:

1. Primary prevention of CAV in HT recipients should include strict control of cardiovascular risk factors (hypertension, diabetes, hyperlipidemia, smoking, obesity) as well as strategies for the prevention of CMV infection.

   Level of Evidence: C.

2. In HT recipients, statin therapy has been shown to reduce CAV and improve long-term outcomes regardless of lipid levels and should be considered for all HT recipients (adult and pediatric).

   Level of Evidence: A.

3. Annual or biannual coronary angiography should be considered to assess the development of CAV. Patients free of CAV at 3 to 5 years after HT, especially those with renal insufficiency, may undergo less frequent invasive evaluation.

   Level of Evidence: C.

4. Follow-up coronary angiography is recommended at 6 months after a PCI because of high restenosis rates in HT recipients.

   Level of evidence: C.

5. Selective coronary angiography is the investigation of choice for the diagnosis of CAV in pediatric HT recipients. It should be performed at yearly or biannual intervals.

   Level of Evidence: C.

Class IIa:

1. A baseline coronary angiogram at 4 to 6 weeks after HT may be considered to exclude donor CAD.

   Level of Evidence: C.

2. IVUS in conjunction with coronary angiography with a baseline study at 4 to 6 weeks and at 1 year after HT is an option to exclude donor CAD, to detect rapidly progressive CAV, and provide prognostic information.

   Level of Evidence: B.

3. In HT recipients with established CAV, the substitution of MMF or AZA with a PSI can be considered.

   Level of Evidence: B.

4. A PSI can been used in pediatric HT recipients who develop CAV, but the effect of PSIs on the progression of CAV in children is unknown.

   Level of Evidence: C.

5. IVUS can be safely used in older pediatric HT recipients to assess CAV.

   Level of Evidence: C.

6. Evaluation of CFR in conjunction with coronary angiography may be useful for the detection of small-vessel CAD, which is a manifestation of CAV.

   Level of Evidence: C.

7. Treadmill or DSE and myocardial perfusion imaging may all be useful for the detection of CAV in HT recipients unable to undergo invasive evaluation. Non-invasive testing for CAV is technically possible in children.

   Level of Evidence: B.

8. PCI with drug-eluting stents is recommended in both adults and children with CAV and offers short-term palliation for appropriate discrete lesions.

   Level of Evidence: C.

9. Surgical revascularization in HT recipients with CAV is an option in highly selected patients who have lesions amenable to surgical revascularization.

   Level of Evidence: C.

10. Cardiac retransplantation may be considered in patients with severe CAV and absence of contraindications for repeat HT.

    Level of Evidence: C.

Class IIb:

1. Ultrafast CT for the detection of coronary calcium has been used mostly as an investigational tool for assessing CAV in HT recipients, but is being superseded by advances in CT angiography.

   Level of Evidence: C.

2. CT coronary angiography shows promise in the evaluation of CAV in HT recipients, although higher resting heart rates in these patients limit the technical quality of this study.

   Level of Evidence: C.

Topic 4: Malignancy After Heart Transplantation

Approach to Malignancy After Heart Transplantation

Prevalence and Risk Factors

Malignancy after HT is a leading cause of both morbidity and mortality in the long term,[55] as is the case with other solid organ transplantation. According to the Spanish Post-Heart Transplant Tumor Registry, among 3,393 HT patients with a median follow-up of 5.2 years, the incidence of malignancy over a 20-year period was 14.4%, approximately 50% of which were cutaneous malignancies, 10% lymphomas, and 40% noncutaneous solid cancers other than lymphoma (lung and prostate being most common).[119] In the 2008 ISHLT registry data, the cumulative prevalence of all types of malignancy post-HT in adults was 15.1% (1,389/9,169) in 5-year survivors and 31.9% (592/1,856) in 10-year survivors.[55] There is little data comparing these rates with matched non-transplant controls. A single-center report from Australia compared the risk of developing cancer in cardiopulmonary transplants with that of a non-transplant population and showed a 26.2-, 21-, and 9.3-fold increase, respectively, for the development of lymphoproliferative, head and neck, and lung cancers.[120] The most common malignancies were skin cancers followed by lymphomas. The risk factors for developing malignancy after 5 years in the ISHLT registry data included recipient male gender and increasing recipient age. In a recent report, the 3 most frequent de novo solid malignancies after HT were prostate, lung, and breast cancers.[120] This study concluded that older age and retransplantation increased the risk, but HT recipients did not have a significantly increased frequency of many common malignancies in spite of long-term immunosuppression.

According to early reports from the Cardiac Transplant Research Database (CTRD) (n = 7,283), the risk of fatal malignancy increases progressively with time after HT.[121] Risk factors for fatal malignancies were a history of pre-transplant malignancy and older age, especially age $\geq$ 60 years.[121-123]

In the pediatric age group, almost all malignancies have been lymphomas. A malignancy is likely to occur in 8% of pediatric HT recipients by 10 years.[124] In a multi-institutional study of lymphoma, 5% of 1184 primary pediatric HT recipients developed post-transplant lymphoproliferative disorder (PTLD).[41] Mean time to PTLD was 23.8 months. Probability of freedom from PTLD was 98%, 94%, and 92% at 1 year, 3 years, and 5 years, respectively, and probability of survival after diagnosis was 75%, 68%, and 67% at 1 year, 3 years, and 5 years, respectively.[41]

Role of Immunosuppression

Chronic immunosuppression and induction therapy have been implicated as risk factors for malignancy. In an analysis of ISHLT Registry data, use of MMF was associated with a significantly lower risk of developing malignancy compared to AZA.[125]

The non-Hodgkin's lymphoma termed PTLD is unusual in immunologically intact individuals and is a serious complication of long-term immunosuppression after solid organ transplantation. Most PTLDs are of B-cell origin and associated with Epstein-Barr virus (EBV) in both children and adults. Reduction of immunosuppression has been used successfully as adjuvant therapy for PTLD.

Because the management of these malignancies can be different than that for more "ordinary" lymphomas, it should initially be pursued at the transplant center by physicians familiar with transplant-related malignancies. In children, most PTLDs occur in EBV-negative recipients of an EBV-positive donor organ who undergo seroconversion after transplantation. Routine EBV surveillance by quantitative polymerase chain reaction (PCR) helps to identify subjects at risk and allows an earlier diagnosis of EBV-mediated PTLD.

Screening and Follow-up

Recommendations for malignancy prevention and screening are highly variable and there is little data upon which to base recommendations after HT.[126] General recommendations to decrease risk of malignancy include individualization and minimization of immunosuppression when safe. Many clinicians aim at avoidance or restricted use of cytolytic therapy in the early post-operative period because induction agents have been associated with an increased risk of lymphoma if used without antiviral prophylaxis.[127] In solid organ transplants other than HT, PSIs appear to be associated with lower PTLD rates.[128] In addition, it is important to educate patients about sun protection, skin self-examination, and signs of skin cancer. Although skin cancers can usually be successfully cured with early detection and removal, squamous cell carcinomas can occasionally have a malignant course in transplant recipients.

Cancer screening recommendations for the common malignancies are similar to those for non-immunosuppressed individuals and include mammography, Papanicolau (PAP) smear, colonoscopy, prostate-specific antigen (PSA) measurement, physical examination for adenopathy or abnormal masses, chest X-ray evaluation for lung masses or

mediastinal adenopathy, and annual detailed dermatological evaluation.

Standard therapy (chemotherapy, radiation therapy, surgery) is recommended for cancers unlikely to be related to immunosuppression. Cardiotoxic chemotherapies can be used, but require strict attention to dose limitations and cardiac follow-up evaluations. Minimization of immunosuppression (often with acceptance of lower CNI levels and/or decreased MMF doses) is important when safe and feasible. Although evidence is lacking, anti-viral therapy is commonly recommended for EBV-related malignancies. Reduction of immunosuppression is typically the first therapeutic measure. Rituximab is an effective treatment for PTLD, and it is generally well-tolerated. It is unknown whether early introduction of rituximab improves prognosis.[129]

Recommendations on the Approach to Malignancy After Heart Transplantation[119, 125, 126, 129]:

Class I:

1. Recommendations regarding screening for breast, colon, and prostate cancer in the general population should also be followed in HT recipients.

   Level of Evidence: C.

2. It is recommended that HT recipients have close skin cancer surveillance, including education on preventive measures and yearly dermatological exams.

   Level of Evidence: C.

3. Initial evaluation and therapeutic plan for PTLD in HT recipients should be done at the transplant center by physicians familiar with transplant-associated malignancies.

   Level of Evidence: C.

4. There is no evidence to support a reduction in immunosuppression in patients with solid tumors unrelated to the lymphoid system. Maintenance immunosuppression should be continued unless there are specific reasons to reduce certain drugs, such as reduction of bone marrow suppressive agents if leucopenia occurs.

   Level of Evidence: C.

Class IIa:

1. Chronic immunosuppression should be minimized in HT recipients as possible, particularly in patients at high risk for malignancy.

   Level of Evidence: C.

Topic 5: Chronic Kidney Disease After Heart Transplantation

Chronic kidney disease (CKD) develops frequently after HT and is associated with substantially increased morbidity and mortality. In the largest study of CKD after solid-organ transplantation, CKD was defined as an estimated glomerular filtration rate (GFR) of < 30 mL/min/1.73m^2, calculated with the 4-variable Modification of Diet in Renal Disease (MDRD) equation.[9] Ojo et al. used this definition to analyze data obtained from the Scientific Registry of Transplant Recipients (SRTR) regarding recipients of heart, lung, heart-lung, liver, or intestine transplants in the US between 1990 and 2000. The overall prevalence of CKD at 5 years after HT was 10.9%. In the same study, CKD was associated with a more than a 4-fold increase in mortality. Mortality risk was highest for patients who were on dialysis.

Mild to moderate renal insufficiency is common in pediatric HT recipients, with a widely variable reported prevalence ranging between 7% and 85%.[41, 130-133] The severity of CKD increases rapidly in the first year after HT and more gradually, thereafter. Studies of CKD in children after HT are complicated by lack of uniform definitions, methodologies for measurement of GFR, and approach to treatment. The 2 largest pediatric registries define severe renal dysfunction as a sCr > 2.5 mg/dL, requiring dialysis or renal transplantation, and report an incidence of approximately 12% at 10 years.[41, 131] These registry data may underestimate CKD in younger patients and those with low muscle mass in whom significant renal compromise occurs at lower sCr levels. According to 1 report, there is a 9-fold increase in risk of death in patients with versus those without severe renal dysfunction.[131]

The typical development of CKD in non-renal transplant recipients usually manifests as a large decrease in the GFR in the first 6 post-operative months, often by 30% to 50%.[134] Thereafter, the GFR stabilizes or decreases at a slower pace. Typically, symptoms are lacking and there is bland urine sediment. In a single-center study of 233 HT recipients, an early 30% drop in creatinine clearance (CrCL) within the first year was associated with a 3-fold increase in the risk of chronic dialysis and death beyond the first post-operative year.

Risk factors for CKD after HT include: (1) traditional risk factors for renal disease (systemic hypertension, atherosclerotic cardiovascular disease, diabetes mellitus, and advancing age); (2) female gender;[9] (3) year of transplantation,[9] due to higher CNI levels before 1993; (4) pre-operative kidney dysfunction. In a retrospective cohort study of HT recipients, more than one-third had stage

≥ 3 CKD before transplantation.[135] In this study, pre-existing renal disease was a strong risk factor for peri-operative acute renal failure requiring dialysis. In addition, HT recipients often suffer from systemic atherosclerosis involving small and large renal vessels,[136-138] diabetes and hypertension. In advanced heart failure, low cardiac output results in renal hypoperfusion. In 1 study, a large proportion of HT candidates had histologic evidence of advanced arteriolar hyalinosis and obsolescent glomeruli.[138] Chronic glomerular hypoxia associated with cyclosporinenotic congenital cardiac disorders and chronic lung disease has been associated with focal segmental glomerulosclerosis (FSGS).[139] It should be noted that reliance on sCr alone to assess pre-operative kidney function typically leads to overestimation of renal function, particularly in patients with malnutrition, low muscle mass, and edema.[140] The utility of pre-transplant kidney biopsy to assess the presence and severity of intrinsic renal disease not reversible with transplant is not established. Involvement of nephrologists in the evaluation of transplant candidates with multiple comorbidities is advisable; (5) peri-operative acute renal failure (ARF): intra-operative risk factors for ARF include hypotension, aortic cross-clamp, atheroembolism, and hemolysis due to extracorporeal circulation. Post-operative risk factors for ARF include hemodynamic instability, right ventricular (RV) failure, the use of pressor agents and/or nephrotoxic drugs, aggressive diuresis, and sepsis.[134, 141] In 1 single-center study of 756 HT recipients, the incidence of post-operative ARF requiring dialysis was 5.8%.[135] In this study, sCr level, albuminemia, insulin-requiring diabetes, and cardiopulmonary bypass (CPB) time were independent predictors of post-operative ARF requiring dialysis. In the same study, the post-operative mortality rate was 50% in patients with ARF requiring dialysis compared with 1.4% in patients without ARF requiring dialysis. In addition ARF requiring dialysis was associated with greater cardiac, neurological, and infectious morbidity; (6) CNI nephrotoxicity: cyclosporine and TAC have inherent nephrotoxicity leading to various renal syndromes (oligoanuric ARF, CKD, type IV or hyperkalemic renal tubular acidosis, thrombotic microangiopathy).[139] The CNIs cause concentration-related renal vasoconstriction, GFR reduction, elevated mean arterial pressure, and albumin excretion.[142] Over time, these perturbations result in progressive arteriolopathy with glomerular ischemic collapse and tubulointerstitial fibrosis. Calcium channel blockers reduce the degree of afferent arteriole vasoconstriction induced by CNIs and have been shown to enhance renal blood flow and prevent the fall in GFR associated with CYA toxicity in kidney transplant recipients.[143] In a retrospective study, conversion of HT patients from ACEI-based antihypertensive therapy to calcium channel blockers was associated with an improvement in renal function.[144] On the other hand, there is a large body of evidence indicating that angiotensin II plays a major role in the chronic nephrotoxic effect of CNIs;[145, 146] (7) polyomavirus BK infection, although the[147, 148] contribution of this virus' to CKD in non-renal organ transplant recipients remains unclear.[149]

In a single-center series of 24 HT recipients, renal biopsy showed hypertensive nephrosclerosis in 30%, FSGS in 16%, diabetic nephropathy in 6%, and CNI-mediated lesions in 60%.[150]

As in adults, renal damage in pediatric HT recipients may predate transplantation. Low cardiac output and acute peri-operative renal failure contributes to this renal damage. The chronic use of CNI and the high incidence of hypertension, 69% at 8 years, contributes to ongoing renal injury[5]. African American race, diagnosis of hypertrophic cardiomyopathy, previous HT and need for intensive care unit (ICU) care and extracorporeal membrane oxygenation (ECMO) pre-operatively increase the risk of reperfusion injury (RI).[130, 131]

The consequences of CKD in HT recipients resemble those in the general population with kidney disease: accelerated cardiovascular disease, sodium retention, hypertension, anemia, and bone disease. Hypertension is already very common after HT, occurring in > 70% of patients.[151] Anemia in HT recipients with CKD can have multiple causes. In addition to erythropoietin deficiency, contributory factors can include marrow suppression from the immunosuppressive agents such as AZA, MMF and SRL, as well as other patient comorbidities.[152-154] The prevalence of CKD-related bone disease in solid organ transplant recipients has not been well studied.

Kidney transplantation appears to be the best therapeutic option for HT recipients with end-stage renal disease. SRTR data demonstrates a significantly lower mortality compared with dialysis in previous non-renal organ recipients.[9] In a very small single-center study, survival rates for HT recipients were worse for peritoneal dialysis (PD) than for hemodialysis (HD), although the referral to PD of unstable patients with failing HT may have contributed to the results.[155] In a study of 16 patients, the survival of HT recipients on HD was similar to that of non-transplant patients.[156]

Diagnosis and Treatment of Chronic Kidney Disease in Heart Transplant Recipients

The following recommendations are based on the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guidelines on the evaluation

and management of CKD.[157-168] It should be noted, however, that the principles of CKD management described in the KDOQI guidelines have not been tested and validated in HT recipients.

Recommendations on Chronic Kidney Disease After Heart Transplantation[44-47, 130, 131, 134, 135, 139, 141, 142, 146, 147, 149, 152]:

Class I:

1. Estimation of GFR with the MDRD equation, urinalysis, and spot urine albumin/creatinine ratio should be obtained at least yearly after HT. Measurement of sCr for estimation of GFR should be obtained more often in patients with GFR < 60 mL/min/1.73 m^2, and/or fast GFR decline in the past (> 4 mL/min/1.73 m^2 per year).

   Level of Evidence: C.

2. Although in children there is no consensus on the optimal method to estimate GFR, this measurement should be done and a urinalysis obtained at least yearly in pediatric HT recipients.

   Level of Evidence: C.

3. HT recipients with an estimated GFR < 30 mL/min/1.73 m^2, proteinuria > 500 mg/day (or urine albumin/creatinine ratio > 500 mg/g), or rapidly declining GFR (> 4 mL/min/1.73 m^2 per year), should be referred to a nephrologist for management of metabolic abnormalities and other complications of renal insufficiency and consideration of renal transplantation.

   Level of Evidence: C.

4. In all HT recipients (adult and pediatric) with CKD, CNI exposure should be lowered to the minimum level required for effective immunosuppression. In patients taking AZA, this may be achieved by conversion of AZA to MMF.

   Level of Evidence: B.

5. Due to the potential for precipitating rejection, CNI free regimens should be used with caution in HT recipients with significant renal insufficiency which persists despite CNI reduction.

   Level of Evidence: C.

6. In pediatric HT recipients, CS minimization or withdrawal should be attempted to avoid hypertension and subsequent CKD, as long as there is no clinical rejection. There is no strong data in adult HT recipients.

   Level of Evidence: B.

7. Interventions that have been proven to slow the progression of CKD in the general population should be considered in all HT recipients. These include strict glucose and blood pressure control and use of an ACEI or angiotensin receptor blocker (ARB). The American Diabetes Association or the International Diabetes Federation Guidelines should be used to manage diabetes. Blood pressure should be treated according to the Joint National Committee VII or the European Society of Cardiology 2007 Guidelines.

   Level of Evidence: C.

8. In pediatric HT recipients, diabetes is rare. In contrast hypertension is common and adequate blood pressure control with a calcium channel blocker or ACEI is warranted to avoid CKD.

   Level of Evidence: C.

9. Hemoglobin levels should be measured at least annually in all HT patients with CKD. If anemia (hemoglobin [Hgb] < 13.5 g/dL in adult males, Hgb < 12 g/dL in adult females) is detected, iron status should be addressed and erythropoiesis-stimulating agents should be used to maintain Hgb levels between 11 and 13 g/dL.

   Level of Evidence: C.

10. Kidney transplantation should be considered the treatment of choice for all HT recipients (adult and pediatric) with end-stage renal disease who are appropriate candidates. Living donation should be considered.

    Level of Evidence: C.

Class IIa:

1. Calcium channel blockers should be considered the anti-hypertensive drug of choice when optimal blood pressure control cannot be achieved with ACEI/ARB, or when these drugs are contraindicated in HT recipients.

   Level of Evidence: C.

Topic 6: Management of Diabetes Mellitus After Heart Transplantation

Prevalence

Diabetes is common in adult HT recipients and is associated with complications including CAV, infection and graft loss. Recent ISHLT registry data show high rates of recipient diabetes mellitus (22%) before transplant.[169] Studies have shown that the cumulative incidence of diabetes in adult HT recipients may be as high as 32% at 5 years.[169] The incidence in pediatric HT recipients is 5% at 5 years.[170]

Pre-transplant Risk Factors

Risk factors for having diabetes pre-transplant are well recognized and include a family history of diabetes, glucose intolerance, and the metabolic syndrome.[171]

Post-transplant Risk Factors for New Onset Diabetes Mellitus

Introduction of the immunosuppressive regimen is the major new risk factor for diabetes in the post-transplant period. Selection of an appropriate regimen should take into account the patient's diabetes risk profile and the increased risk for development of diabetes resulting from the use of immunosuppressive drugs, balancing risk of diabetes with effective immunosuppression.[172]

CSs are associated with the highest risk of post-transplant diabetes and, therefore, attempts should be made to reduce the dose as early as possible in high risk patients. Small studies describing CS weaning protocols and CS avoidance have been described.[173]

The CNIs CYA and TAC both have diabetogenic effects. In an older small, single-center study, a trend toward a higher incidence of post-transplant diabetes was observed in HT recipients receiving TAC versus CYA.[174] More recent studies also confirm that TAC may be more diabetogenic than CYA.[95, 96] TAC is also more diabetogenic in pediatric recipients[175] and people of African descent. Changes in insulin sensitivity as well as in insulin secretion probably both contribute to CNI-induced hyperglycemia.[176] There are limited data regarding other immunosuppressive agents.

Guidelines and Recommendations

Management of post-transplant diabetes generally should conform to the guidelines for treatment of type 2 diabetes mellitus in the general population.[176] In 2003, the International Consensus Guidelines on new onset diabetes after transplantation were published.[177] These guidelines were updated in 2004.[178] In addition, guidelines for The Standards of Medical Care in Diabetes have been published by the American Diabetes Association (ADA) Position Statement in 2006.[179] The definition, diagnosis and therapy of post-transplant diabetes should be based on the above publications since there is limited data on diabetes therapy focusing only on HT recipients. The medical management of diabetes after transplantation should be a joint effort of endocrinologists and transplant physicians following these general guidelines.

Cardiovascular risk factors including post-transplant diabetes should be closely monitored and treated because of the risk of morbidity including cardiac allograft vasculopathy.[180, 181]

Recommendations for the Management of Diabetes After HT[169, 171, 175-178]:

Class I:

1. Prevention, early detection and appropriate therapy of diabetes should be considered as an important component of patient care after HT.

   Level of Evidence: C.

2. Patients should be periodically screened for diabetes after HT by measuring fasting plasma glucose levels or with an oral glucose tolerance test (more sensitive screening test for pre-diabetic state) and HbA1c determination, as appropriate. The frequency of screening will depend on risk factors and immunosuppressive therapy.

   Level of Evidence: C.

3. Therapies for short-term peri-operative and long-term chronic glycemic control in HT recipients should be based on ADA recommendations.

   Level of Evidence: C.

4. HT recipients with diabetes should be counseled regarding weight control, diet/nutrition and exercise.

   Level of Evidence: C.

5. Pre-HT risk factors should be assessed and diabetogenic immunosuppressive medications should be minimized whenever possible in HT recipients.

   Level of Evidence: C.

6. CS-sparing regimens and decreased CNI doses should be used as appropriate to prevent diabetes in HT recipients.

   Level of Evidence: C.

7. Associated cardiovascular risk factors (in addition to diabetes) such as hyperlipidemia and hypertension should be managed aggressively in HT recipients. Annual measurements of lipids levels should be performed according to ADA recommendations.

   Level of Evidence: C.

8. Annual screening should be performed for diabetic complications (ophthalmology, podiatry, peripheral vascular disease, etc.) in HT recipients with diabetes.

   Level of Evidence: C.

Class IIa:

1. An endocrinology consultation may be considered when a pre-diabetic state or diabetes is diagnosed in a HT recipient.

   Level of Evidence: C.

Topic 7: Other Complications of Chronic Immunosuppressive Drugs

There are many additional complications of immunosuppressive agents in both adults and children after HT that should be mentioned. Complications are discussed here for the following immunosuppressive agents: CNIs (TAC and CYA), mTOR inhibitors (SRL and EVL), MMF, and CS.

CNIs and mTOR inhibitors

Each of the immunosuppressive drugs used after HT has numerous individual as well as class-specific adverse effects, which can sometimes be increased by concomitant use of other immunosuppression agents. The major and most common of such adverse effects, including CKD and malignancies, including lymphoproliferative disorders, are discussed in other sections. We will review the other documented adverse effects associated with these agents and these are summarized in Table 2. When complications of CNIs prove insurmountable (e.g., advancing PTLD or refractory infection), a change from CNI to mTOR inhibitors may be considered after 3 months post-operatively and resolution of all active wound healing.[182, 183] As many adverse effects are dose dependent, it is recommend that close follow-up of blood levels of both CNI and mTOR inhibitors be performed, especially in the early post-operative period. CNIs are routinely dosed 12 hours apart while mTOR inhibitors are routinely dosed once daily, with trough levels collected 30 minutes before the morning dose. The younger patient may require dosing more frequently because of having shorter drug half-lives.[184]

Many of the adverse effects noted in Table 2 are poorly characterized and idiosyncratic reactions may occur, the incidence or prevalence of which is unclear. A high degree of vigilance for the occurrence of such adverse effects is appropriate. Most of these complications are rare and attribution to the drug is a diagnosis of exclusion. Aside from the common toxicities described elsewhere in these guidelines, peripheral neuropathy, and alopecia are most commonly attributed to CNI whereas impaired wound healing, mouth ulcers, peripheral edema, and pulmonary toxicity are most commonly seen with mTOR antagonists. Hirsutism and gingival hyperplasia are commonly seen with CYA, especially in young patients and can be very bothersome.

Mycophenolate Mofetil

MMF is the most frequently used anti-proliferative agent in HT recipients.[55] Side effects of MMF are listed in Table 2. In a multicenter, randomized, controlled clinical trial of 334 primary HT recipients, a combination of TAC and MMF resulted in an improved side effect profile as compared to a combination of TAC and SRL or CYA and MMF.[185] Notably, while adverse events were generally comparable among the 3 groups, sCr and triglyceride levels were lowest in the TAC and MMF group. Lastly, retrospectively done multivariate analyses of 3,895 adult HT recipients enrolled in the ISLHT Registry revealed a significantly lower risk of developing malignancy in patients receiving MMF in standard immunosuppression protocols.[126]

Dose reductions, use of the enteric-coated preparation, occasional discontinuation, and use of drugs to protect the GI tract have been used to treat GI complications of MMF.[186] Notably, findings from a multicenter trial (n = 154) randomizing patients to either MMF or enteric-coated mycophenolate sodium (EC-MPS) demonstrated similar side effect profiles for each group with a trend toward less diarrhea in patients receiving EC-MPS.[187] Importantly, authors of a single-site retrospective study (n = 182) of HT recipients receiving MMF identified increased rates of sustained rejection with MMF dose reduction and suggested use of enteric-coated formulations of MMF instead of dose reduction and close follow-up of these HT recipients, including more frequent monitoring of MPA levels.[188] More research is needed, including a prospective evaluation of the relationship between GI intolerance and rates of rejection.

Corticosteroids

The CSs have been used as immunosuppression after HT for 4 decades and remain a component of immunosuppression (at least early post-transplant) in combination with CNI and anti-proliferative agents. The most recent ISHLT registry data confirm the ongoing use of prednisone, with 73% and 54% of patients on CSs at 1 and 5 years after HT, respectively.[55] The adverse effects of CSs are well known, and are listed in Table 2. Weaning of CSs is a common clinical practice after transplantation and can contribute to reversal of their adverse effects as outlined in Topic 1. Early CS-weaning protocols described reduced rates of GI complications,[189] diabetes mellitus,[190] and rejection,[191] and increased survival[191, 192] in patients weaned versus patients not weaned from CSs. Although another review from the same era reported no difference in the rates of diabetes, infection, and survival, it did demonstrate decreased acute rejection and malignancy rates in patients on CYA and AZA who were weaned versus those not weaned from CSs.[193] One of the largest prospective studies of CS weaning in kidney and HT recipients demonstrated significantly lower rates of cataracts and osteoporosis in patients withdrawn from CSs during the first year post-transplant.[194] Additionally, other studies have

reported successful reversal of osteoporosis with prednisone weaning and osteoporosis prophylaxis.[195, 196]

Recommendations on the Management of Various Complications of Chronic Immunosuppression[182, 183, 186-188, 191, 195-233]:

(See Table 2)

Class I:

1. Recommendations for addressing other complications of immunosuppression include regular screening for adverse events, minimizing drug doses, drug substitution, and drug withdrawal (as previously discussed), as well as initiating targeted therapies for a specific complication. For example, anti-hyperuricemic therapy and concurrent risk reduction may be used to prevent recurrent attacks of gout, while acquired cataracts require surgical intervention. It is important to assess for contraindications and drug interactions when medically treating complications of immunosuppression.

Level of Evidence: C.

Table 2 Complications of Immunosuppressive Drugs

Drug	Toxicities
Calcineurin inhibitors: cyclosporine and tacrolimus	*Cardiovascular*: hypertension, edema[214] *Neurologic*: headache, tremor, insomnia, hearing loss posterior reversible encephalopathy syndrome Parkinsonism, central and peripheral neuropathy, seizures[206-214] *Hematologic*: anemia, leukopenia, thrombotic microangiopathy, eosinophilia[197, 214, 215] *Dermatologic*: fibrovascular polyps alopecia,[198, 216] hirsutism, gingival hyperplasia[199] *Gastrointestinal*: nausea, diarrhea, steatohepatitis, cholestatic jaundice, colonic malakoplakia, eosinophilic gastroenterocolitis, villous atrophy/food allergies, hepatic veno-occlusive disease[197, 200, 214, 217-220] *Endocrine/metabolic*: hypophosphatemia, hypomagnesemia, hyperglycemia, hyperkalemia, hyperlipemia[214] *Renal*: renal dysfunction / nephropathy[214] *Infection*[214]
Mammalian target of rapamycin inhibitors	*Cardiovascular*: edema, hypertension[214] *Neurologic*: headache, progressive multifocal encephalopathy, optic neuropathy[214, 221] *Hematologic*: anemia, thrombocytopenia, thrombotic microangiopathy, venous thromboses[201, 214, 222, 223] *Respiratory*: dyspnea, pulmonary toxicity, interstitial pneumonitis, BOOP, alveolar proteinosis, alveolar hemorrhage[202, 203, 214, 224, 225] *Endocrine and metabolic*: hypertriglyceridemia, hypercholesterolemia[214] *Dermatologic*: acneiform facial dermatitis, ulcerating rash: perforating collagenosis, wound healing complications: dehiscence, leukocytoclastic vasculitis[204, 226] *Musuloskeletal*: extremity lymphedema (bilateral and unilateral); lingual angioedema; impaired wound healing[182, 183] *Gastrointestinal*: Diarrhea, nausea, vomiting, gastroduodenal ulcer disease; hepatotoxicity[214, 227, 228] *Genitourinary*: urinary tract infection, infertility (oligospermia)[205, 214, 229]
Mycophenolate mofetil	*Infection* (e.g., herpes simplex virus and cytomegalovirus)[187, 230, 231] *Gastrointestinal* (e.g., nausea, constipation, diarrhea, vomiting, dyspepsia, abdominal distension and pain, esophagitis)[187, 230, 231] *Metabolism and nutritional* (e.g., hyperglycemia, hypercholesterolemia, gout)[187, 214] *Cardiovascular* (e.g., hypertension, peripheral edema)[187, 214] *Hematologic* (e.g., leukopenia, thrombocytopenia)[187, 214, 230] *Nervous system* (ex., headache, tremor)[187, 214] *Respiratory* (e.g., dyspnea, respiratory tract infection, cough)[187] *Renal* (e.g., increased BUN and / or creatinine)[214] *Dermatologic* (e.g., rash)[214]
Corticosteroids	*Gastrointestinal* (e.g., peptic ulcer, esophagitis, pancreatitis)[214] *Neuromuscular and skeletal* (e.g., osteoporosis, pathological fractures, muscle mass loss, CS myopathy)[195, 196, 214, 232, 233] *Central nervous system* (e.g., emotional instability, headache)[214] *Dermatologic* (e.g., bruising, thin fragile skin, impaired wound healing)[214] *Endocrine and metabolic derangements* (e.g., diabetes mellitus, hyperlipidemia, fluid retention, growth suppression in children, adrenal suppression, adrenocortical and pituitary unresponsiveness in times of stress, and menstrual irregularities)[214] *Ocular complications* (e.g., glaucoma, cataracts)[214]

Topic 8: Hypertension After Heart Transplantation

Prevalence and Risk Factors

Up to 95% of adult patients suffer from arterial hypertension by 5 years after HT.[234] Hypertension is also present in 69% of children by 8 years after HT.[41] This high incidence of hypertension is primarily due to the use of CNI, with hypertension rates being lower in TAC-treated than in CYA-treated.[234] In one study of 253 HT recipients, variables associated with post-operative hypertension were male recipient and donor, idiopathic dilated cardiomyopathy prior HT, hypercholesterolemia and renal dysfunction after HT.[235] Although the causes of hypertension are less well elucidated in children than in adults, they are also likely to be multi-factorial and with similar relationships to CNI and abnormal neural-hormonal reflexes. Arterial rigidity appears to be increased[236] and baro-receptors abnormal.[237]

In a study of 33 adult HT recipients, 24-hour ambulatory blood pressure monitoring demonstrated that conventional blood pressure measurement underestimates the incidence of hypertension after HT in both children and adults.[238] Such measurements generally show consistent elevation of diastolic blood pressure and of night time systolic blood pressure.[239] While CSs remain widely used in pediatric HT, a high prevalence of hypertension was also found in patients on a CS-free regime.[239] High levels of CNIs and a combination of lower levels of CNI, CS and SRL have also been associated with pediatric HT hypertension.[240]

Therapy

There are no large randomized trials on the effects of anti-hypertensive therapy on outcomes after HT. A small, prospective, randomized study compared lisinopril with diltiazem for 1 year and found no difference in blood pressure control, renal function or side effects between the 2 agents.[241] A study of 247 HT patients showed hypertension to be present in 33.3% before HT and 71.1% at some time afterwards. The average number of drugs used to control hypertension was 1.3. A single drug was used in 72.9% of patients and the most commonly used medications were calcium channel blockers (63.2%), followed by ACEIs (20%), and ARBs (15.8%).[235]

In another study 38 CYA-treated HT recipients were randomized to either placebo or amlodipine 2.5 mg/day. Study drug dose was gradually increased to 10 mg/day as tolerated. Early initiation of amlodipine after HT was associated with adequate blood pressure control and preservation of renal function for 1 year after HT.[242] The occurrence of lower extremity edema, however, remains often bothersome side effect of this drug.

Little evidence exists on what might be the best treatment for pediatric HT.[240] As in adults, calcium channel blockers and ACEIs are the most frequently used agents.

Recommendations on the Management of Hypertension After Heart Transplantation[234-236, 238, 240, 241]:

Class I:

1. Because in HT recipients anti-hypertensive therapy has benefits similar to those in the general population, hypertension after HT should be treated to achieve the same goals recommended for the general population.

   Level of Evidence: C.

2. Lifestyle modifications including weight loss, low sodium diet, and exercise are appropriate adjuncts to facilitate control of blood pressure in HT recipients.

   Level of Evidence: C.

3. Drug choice for treatment of hypertension in HT recipients is empiric and depends on blood pressure responses. Calcium channel blockers are most widely used, but ACEI and ARB may be preferred in diabetics and a 2-drug regimen can include both calcium channel blockers and ACEI/ARB.

   Level of Evidence: C.

4. Modification of risk factors such as diabetes and hyperlipidemia are appropriate as adjunctive treatment for hypertension in HT recipients.

   Level of Evidence: C.

5. Appropriate adjustment of immunosuppressive therapy, especially CS weaning, may be helpful in management of hypertension in HT recipients.

   Level of Evidence: C.

Class IIa:

1. Hypertension is common in both adults and children after HT and can be assessed with ambulatory blood pressure monitoring.

   Level of Evidence: C.

Topic 9: Prophylaxis for Corticosteroid-induced Bone Disease After Heart Transplantation

Bone Disease in Heart Transplant Candidates

Only a minority of patients awaiting HT have normal bone density. In 1 study of 101 patients with New York Heart Association (NYHA) class III and IV heart failure (HF) referred for HT evaluation, osteoporosis at the femoral neck was seen in 19%, and osteopenia in an additional 42%.[243] In another study of 14 patients with HF awaiting HT, 14% had radiological evidence of vertebral compression fractures.[244] Factors associated with HF that may contribute to bone loss include decreased mobility, low serum 25-hydroxyvitamin D (25-OHD),[243] hypogonadism, long-term heparin and/or loop diuretic administration, renal failure, and secondary hyperparathyroidism.[245]

Biphosphonates are considered first-line therapy for postmenopausal osteoporosis,[246] osteoporosis in men,[247] and CS-induced osteoporosis.[248] In these populations biphosphonate therapy clearly increases bone mineral density (BMD) and reduces fractures.

Prophylaxis Against Corticosteroids-induced Bone Disease in Adult and Pediatric Heart Transplant Recipients

Large decreases in BMD at the lumbar spine and femoral neck are observed during the first year after HT.[232, 249] This decrease occurs mainly in the first 3 to 6 months[232] and is probably related to the large doses of CSs used immediately after HT.[250] Post-operatively, lumbar spine BMD typically declines 3% to 10% in the first 6 months, and stabilizes thereafter. Partial recovery of lumbar spine BMD occurs in later years. BMD at the femoral neck similarly decreases 6% to 11% in the first year and stabilizes thereafter. There appears to be less bone loss in more recent years compared with the late 1980s and early 1990s,[251, 252] probably due to lower CS doses.[252]

The incidence of new fractures parallels the timing of the most rapid loss of BMD, with most fractures occurring in the first year after HT.[244, 253-256] Radiographic evidence of vertebral fracture is seen in 12% to 35% of long-term HT recipients.[251-254] The incidence of fractures in the pediatric population is less than in adults. There is minimal data regarding osseous complications in pediatric HT. Chronic illness in childhood, use of medications with negative impact on bone development and post-operative renal dysfunction all contribute to delayed childhood growth and development. Dual-energy X-ray absorptiometry (DEXA) scans to measure BMD is limited in children[257] due to the prevalence of short stature and CKD[258, 259] unless each child is used as his/her own control.

Three prospective, randomized, albeit very small, trials demonstrate the importance of physical activity in restoring BMD in HT recipients.[260-262] On the other hand, replacement doses of calcium and vitamin D do not prevent clinically significant bone loss after HT.[232] However, trials that have demonstrated the efficacy of other medications have generally been conducted in the setting of calcium and vitamin D repletion. Furthermore, the American College of Rheumatology guidelines on the prevention and management of CS-induced osteoporosis recommend calcium and vitamin D supplementation for all patients receiving these medications.[248] Active metabolites of vitamin D (calcidiol, alfacalcidol, and calcitriol) have been shown to reduce post-HT bone loss,[252, 263-266] but are associated with an increased risk of hypercalcemia and hypercalciuria, that may develop anytime during treatment.[252] Biphosphonates are indicated for the prevention of CS-induced osteoporosis,[248] and their anti-resorptive action makes these drugs the obvious choice to prevent the increased bone resorption and rapid bone loss early after HT. In a 1-year, double-placebo, double-blind study in which 149 HT recipients were randomized to either calcitriol (0.5 mcg/day) or alendronate (10 mg/day), in addition to calcium and vitamin D[252] the degree of bone loss and fracture rates did not differ significantly between the intervention groups. However, patients treated with either drug had significantly less bone loss at the hip than controls given calcium and vitamin D. In an extension of this study, BMD remained stable in the second post-operative year, after alendronate and calcitriol were discontinued.[267] In another prospective study, a 3-year treatment of quarterly infusions of 60 mg of pamidronate, combined with calcium and vitamin D, significantly increased lumbar spine BMD and prevented bone loss at the femoral neck in osteoporotic HT recipients.[268] Biphosphonates have also proved an effective treatment for bone loss in long-term HT recipients.[269] Finally, calcitonin has been shown to be ineffective in preventing early post-HT bone loss.[233, 270] Routine use of bisphosphonate therapy in pediatric patients is controversial because of inadequate long-term efficacy and safety data. For this reason, many experts recommend limiting use of these agents to those children with recurrent extremity fractures and symptomatic vertebral collapse. The use of bisphosphonates in children can increase BMD but it is unknown whether this correlates with reduced fractures rates.

Recommendations for the Prophylaxis of Corticosteroid-Induced Bone Disease After Heart Transplantation[37, 244, 245, 250, 252, 253, 261, 262, 264, 267, 269]:

Class I:

1. All adult HT candidates should be screened for pre-existing bone disease, preferably at the time of placement on the waiting list. In adults, baseline BMD should be obtained with a DEXA scan of the lumbar spine and femoral neck.

   Level of Evidence: C.

2. The presence of low BMD or vertebral fractures should prompt evaluation and treatment of correctable secondary causes of osteoporosis, as significant improvement in BMD can be attained during the waiting period for HT. Biphosphonates should be considered the treatment of choice.

   Level of Evidence: C.

3. All HT candidates and recipients should have the recommended daily allowance for calcium (1000-1500 mg, depending on age and menopausal status) and vitamin D (400-1000 IU, or as necessary to maintain serum 25-hydroxyvitamin D levels above 30 ng/mL = 75 nmol/L).

   Level of Evidence: C.

4. After HT, regular weight bearing and muscle strengthening exercises should be encouraged to reduce the risk of falls and fractures and to increase bone density.

   Level of Evidence: B.

5. In pediatric HT recipients, it is important to monitor growth and pubertal development and be alert to the development of signs and symptoms of bone disease.

   Level of Evidence: C.

6. Reduction or withdrawal of CS in pediatric HT recipients should be considered in the absence of preceding rejection with close monitoring for clinical rejection.

   Level of Evidence: B.

7. After HT children should be encouraged to increase physical activity; daily intake of calcium with vitamin D through diet or supplements should meet recommendations for age.

   Level of Evidence: C.

8. All adult HT recipients should begin anti-resorptive therapy with bisphosphonates immediately after HT and continue it at least throughout the first post-operative year.

   Level of Evidence: B.

9. Biphosphonates can be used to treat bone loss in long-term HT recipients, and should be used in addition to calcium and vitamin D.

   Level of Evidence: C.

10. In pediatric HT recipients who have not reached bone maturity, bisphosphonates should be restricted to patients with reduction in bone mass density associated with low trauma fractures or vertebral compression.

    Level of Evidence: B.

Class IIa:

1. It is reasonable to perform spine radiographs in all adult HT candidates to detect existing fractures.

   Level of Evidence: C.

2. After the first post-HT year, if glucocorticoids have been discontinued and BMD is relatively normal (T score $\geq$ 1.5), it is reasonable to stop bisphosphonates, maintaining a high degree of vigilance for osteoporosis.

   Level of Evidence: C.

3. Proximal femur and lumbar spine BMD should be assessed by DEXA scanning in all adult patients 1 year after HT. Thereafter, annual reassessments are wise in patients receiving CS and/or bisphosphonate therapy. However, it should be kept in mind that increases in BMD with bisphosphonates account for a small fraction of their efficacy in preventing bone fractures. It is reasonable to repeat BMD measurement in 2 years in patients with osteopenia and in 3 years in patients with normal bone density. Any clinical suggestion of fracture should prompt bone radiographs.

   Level of Evidence: C.

Class IIb:

1. Active metabolites of vitamin D (calcidiol, alfacalcidol, and calcitriol) should not be regarded as first-line treatment for bone loss after HT. If they are used, frequent monitoring of urine and serum calcium levels is required, as hypercalcemia and hypercalciuria are common and may develop anytime during treatment.

   Level of Evidence: B.

Class III:

1. Calcitonin should not be used to prevent early bone loss after HT.

   Level of Evidence: B.

Gaps in Evidence:

Biphosphonates continue to suppress bone reabsorption after discontinuation of therapy. It is not known, however, if pre-operative administration of these drugs can prevent the increased bone loss that develops after HT with the introduction of CS.

Gaps in Evidence[31]:

The predictive role of BMD measurement for fracture risk is unproven in HT recipients. Although there have been several studies describing a beneficial effect of bisphosphonates and vitamin D analogues on bone density in adult HT recipients, none of these studies has been powered to detect a decrease in fracture rate. In addition, important issues that remain unresolved include which is the optimal bisphosphonate, the route and duration of administration, whether therapy should be continuous or intermittent. More research is also needed to define appropriate indications for bisphosphonate therapy and the optimal agent, dose, and duration of use in pediatric patients.

The potential role in the HT population of the recombinant human parathyroid hormone (teriparatide), a bone forming agent, and strontium ranelate, the first agent to stimulate bone formation while decreasing reabsorption, deserves investigation.

Topic 10: Reproductive Health After Heart Transplantation

Improving survival in HT recipients has prompted increased attention on issues such as the desire of adolescent and adult patients to be involved in romantic relationships and the need to control fertility. The vast majority of the published literature regarding pregnancy and solid organ transplant is derived from renal and liver recipients, with limited data, mostly accumulated through registries, addressing HT recipients. Most male HT recipients maintain normal fertility and there is no evidence of teratogenicity in their offspring.

Pregnancy

Fertility and pregnancy are important issues and often pose complex medical, psychosocial, and ethical problems. Genetic counseling may be helpful for those patients transplanted for congenital heart disease or a familial cardiomyopathy. Ideally, pregnancy should be discouraged during the first post-operative year and thereafter it should be planned so that potentially teratogenic drugs can be stopped and substituted, if necessary, before conception. The physiological changes that occur in pregnancy are generally well tolerated by HT recipients. Comorbid conditions during pregnancy can include: hypertension, diabetes, infection and pre-eclampsia. The risk of rejection during and after pregnancy is significant, and it is important to maintain an adequate level of immunosuppression. Drug blood levels may vary significantly during pregnancy due to changes in blood volume, increased GFR and decreased gastric motility. Thus, increased monitoring frequency of immunosuppressive drug levels is mandatory. Performing surveillance EMB during pregnancy is problematic because of the associated radiation exposure unless done with echocardiographic guidance. Performance of cardiac testing, including EMB and coronary angiography, if not done within the preceding 6 months is recommended before attempting pregnancy. Avoidance of pregnancy is recommended in HT female recipients with CAV and allograft dysfunction

Infants are at greater risk of premature delivery due to an increased likelihood of spontaneous preterm labor and of complications necessitating delivery. Approximately one-third of neonates are small for their gestational age. Knowledge of the long-term graft and patient outcomes are critical to counseling these patients regarding the impact of pregnancy on survival, and ability to participate in child rearing.

Recommendations on Pregnancy After Heart Transplantation[271-273]:

Class I:

1. A multi-disciplinary team, involving specialists in maternal and fetal medicine, cardiology and transplant medicine, anesthesia, neonatology, psychology, genetics, and social service, is important in the care of pregnant HT recipients.

   Level of Evidence: C.

2. The management plan for pregnant HT recipients should be individualized according to the status of the mother and her transplanted heart and is best achieved at the primary transplant institution in collaboration with local or referring physicians.

   Level of Evidence: C.

3. Individual factors in a HT recipient who wishes to become pregnant should be considered, including the risk of acute rejection and infection, review of concomitant therapy that is potentially toxic or teratogenic and review of the adequacy of graft function. After careful consideration of these individual factors, patients should be counseled on the risks of pregnancy and pregnancy discouraged if graft dysfunction and significant CAV are expected to preclude a successful outcome.

   Level of Evidence: C.

4. Pregnancy in a HT recipient should generally not be attempted sooner than 1 year post-operatively.

   Level of Evidence: C.

5. In a HT recipient who wishes to become pregnant baseline tests should be obtained to determine the cardiac status of the patient and should include an ECG and echocardiogram (and coronary angiography if not performed within the previous 6 months) with the option of right heart catheterization and EMB, if clinically indicated.

   Level of Evidence: C.

6. Baseline assessment of renal and liver function should be obtained in a pregnant HT recipient and frequent monitoring of blood pressure, urine cultures and surveillance for preeclampsia and gestational diabetes should be done.

   Level of Evidence: C.

7. Calcineurin inhibitors and CS should be continued in a pregnant HT recipient, but MMF (class D) should be discontinued.

   Level of Evidence: C.

8. Blood levels of CNI should be followed closely during pregnancy due to large fluctuations in levels during the pregnancy-related changes in plasma and interstitial volume and hepatic and renal blood flow.

   Level of Evidence: C.

9. Frequent surveillance for rejection is imperative in a pregnant HT recipient, although surveillance EMB done under fluoroscopy should be avoided. An EMB under echocardiographic guidance or fluoroscopy with leaded patient draping can be performed if necessary.

   Level of Evidence: C.

Class IIb:

1. The use of AZA (also Class D), as a substitute for MMF, is somewhat controversial and avoidance of both agents in a pregnant HT recipient should be decided on the basis of the balance of maternal and fetal risk.

   Level of Evidence: C.

Class III:

1. It is uncertain whether the potential risks of drug exposure for the infant outweigh the benefits of breastfeeding, which is therefore not recommended for HT recipients.

   Level of Evidence: C.

Contraception

Evaluation of the risks and benefits of combined hormonal contraception must take into consideration the patient's risk of an unintentional pregnancy and the potential outcomes of such a pregnancy for both the mother and child. In adults, the option of personal or partner sterilization may be considered. In adolescents, the most effective method of birth control is probably hormonal contraception. However, it is important to consider the side effects of the hormonal methods. Hormonal contraception with a combination of estrogen and progesterone can be given orally, or using a weekly patch or a vaginal ring. Hormonal contraception containing only progesterone can be given orally or by injection. Depo-medroxyprogesterone acetate given intramuscularly every 3 months is extremely effective for the prevention of pregnancy. It can cause irregular bleeding and weight gain early in its use, and can cause a decrease in bone density. Intrauterine devices have generally been avoided in HT recipients due to the risk of infection, although no prospective studies have been done on this subject. Barrier methods protect against unwanted pregnancy and sexually transmitted diseases without risk to the HT recipient.

Recommendations for Contraception After Heart Transplantation[274, 275]:

Class I:

1. Before prescribing combination hormonal contraception a HT recipient should be screened for risk factors for a hypercoaguable state (a strong family or personal history of thromboembolic events).

   Level of Evidence: C.

2. Combined hormonal contraception inhibits the CYP-3A4 pathway and immunosuppressant drug blood levels should be monitored carefully when starting this therapy in HT recipients.

   Level of Evidence: C.

3. Barrier methods provide inadequate pregnancy protection and should be used as an adjunct to other methods in HT recipients. They should be recommended for all sexually active adolescents for sexually transmitted infection (STI) prevention.

   Level of Evidence: B.

Class IIb:

1. Intrauterine devices (IUD) have been generally not recommended in HT recipients and in particular in nulliparous patients because of the increased risk of IUD expulsion in nulliparous women and because of concerns

regarding increased risk of pelvic inflammatory infection and infertility.

Level of Evidence: C.

Class III:

1. Depo-medroxyprogesterone acetate has been associated with decreased bone density and therefore it is not routinely recommended for HT recipients.

   Level of Evidence: C.

2. Hormonal contraception should not be prescribed in HT recipients who have significant hypertension, known CAV, estrogen sensitive cancers or active liver disease.

   Level of Evidence: C.

Sexually Transmitted Infections

The routine monitoring of HT recipients for rejection, malignancy and infection must include evaluation of acquired STI. Education of sexually active adults, and particularly adolescents, about "safe sex" and the potential need for screening for STIs, especially in those with multiple partners, should be paramount.

Recommendations for the Management of Sexually Transmitted Infections[276]:

Class I:

1. Clinicians should obtain a confidential sexual history from adolescent HT recipients and may consider routine referral to an adolescent medicine specialist who will provide thorough and confidential reproductive health care.

   Level of Evidence: C.

2. Sexually active adolescents and adult HT recipients with multiple partners should be advised to undergo screening for STI, including a complete anogenital exam to screen for anogenital warts, molluscum, herpes simplex virus (HSV), or other lesions at an appropriate clinic at regular intervals.

   Level of Evidence: C.

3. A complaint of genitourinary symptoms or disclosure of high risk behavior should trigger a full evaluation for STI in HT recipients. Genitourinary symptoms may also be an indication for empiric antimicrobial therapy while awaiting results of STI screening.

   Level of Evidence: C.

4. The quadrivalent human papillomavirus (HPV) vaccine may prevent persistent HPV infection, cervical and vulvovaginal cancer precursor lesions, and genital warts secondary to HPV types 6, 11, 16, and 18. Women should receive all 3 doses before HT. There is no contraindication to administering the vaccine to women after HT, although no studies have confirmed immunogenicity or efficacy in this population.

   Level of Evidence: C.

Erectile Dysfunction

Erectile dysfunction (ED) frequently occurs after HT. Before recommending specific therapy, possible iatrogenic and psychological causes should be sought and addressed. Therapy with phosphodiesterase (PDE) 5 inhibitors or intracavernous injections of prostaglandin E1 is acceptable and safe with the same precautions recommended for non-transplant patients.[277]

Recommendations for the Management of Erectile Dysfunction After Heart Transplantation[277]:

Class I:

1. Possible iatrogenic causes of ED should be identified in HT recipients and alternative medications should be used where possible.

   Level of Evidence: C.

2. In HT recipients with ED, use of phosphodiesterase inhibitors can be considered. Concomitant nitrate therapy is contraindicated similarly to the general population.

   Level of Evidence: C.

3. In HT recipients with ED, consider referral to an ED specialist for possible intra-cavernous injections of prostaglandin E1 if PDE inhibitors are ineffective or contraindicated.

   Level of Evidence: C.

Topic 11: Exercise and Physical Rehabilitation After Heart Transplantation

Exercise capacity is known to be decreased after HT and this is related to factors both before and after transplant surgery.[278] Patients with severe chronic HF awaiting HT not only have abnormal cardiovascular responses to exercise but they also develop maladaptation in skeletal muscle including atrophy, decreased mitochrondial content, a shift toward fatigue-sensitive type II b fibers, a decrease in oxidative enzymes, and an increase in glycolytic enzymes, all of which contribute to exercise intolerance. In addition, many patients also develop deconditioning due to prolonged hospitalizations and limited physical capacity after implantation of ventricular assist devices. These skeletal muscle abnormalities are not readily reversed after HT and contribute to diminished exercise capacity early after HT. The technique of HT with

denervation of the heart also contributes to diminished aerobic capacity Adults after HT usually have values of peak oxygen consumption (VO_2) that do not exceed 60% of the value for healthy age-matched control subjects.[279] Several factors have been shown to contribute to diminished exercise capacity including denervation with chronotropic incompetence with a narrow heart rate reserve, LV diastolic dysfunction with a diminished stroke volume response to exercise, and high peripheral vascular resistance.

Despite restored cardiac pump function, patients after HT retain several of the abnormalities in the peripheral circulation and skeletal muscle seen with chronic heart failure. Chronic immunosuppression with CSs and CNIs may also contribute to diminished skeletal muscle function.[280] Although there is some improvement in exercise capacity over time after HT, these factors prolong recovery from surgery and hospitalization and diminished aerobic capacity may contribute to several medical conditions including hypertension, type 2 diabetes, obesity, metabolic bone disease, and CAV.

Uncontrolled studies have demonstrated that exercise training, both early and late after HT, improved exercise capacity.[281-283] Most studies involved small numbers of patients who were carefully selected. They demonstrated that exercise training could increase peak VO_2 by 27% to 33%. In certain studies, there were additional favorable adaptations including an increase in peak exercise heart rate, decreases in heart rate at rest, and during submaximal exercise, and decreases in systemic blood pressure at rest and during exercise. Most studies did not standardize the timing of exercise training after HT and there were differences in the duration and composition of the exercise programs. There is 1 randomized, controlled trial that investigated the effect of exercise training beginning 2 weeks after HT.[284] An exercise program was individualized to each patient and included aerobic exercise, strengthening and flexibility exercises. After 6 months, patients in both the control and exercise groups improved their peak exercise VO_2 and workload with significantly greater improvements in the exercise group. Patients who underwent exercise training also had a decrease in the ventilatory equivalent/carbon dioxide production (V_E/VCO_2) ratio at peak exercise and a greater improvement in the sitting-to-standing heart rate, a measure of skeletal muscle strength and endurance. There were no significant increases in peak exercise heart rate or decreases in heart rate or systemic blood pressure at rest. In addition, exercise training was demonstrated to be safe in these patients with no increase incidence of cardiac rejection, infection, or other cardiovascular adverse effects. The results of this study along with those of previous non-controlled trials demonstrated the ability of early exercise training to improve functional capacity in adult HT patients.

The mechanisms responsible for the improvement in exercise capacity have not been well defined but it appears that re-innervation and thus improvement in cardiac function during exercise do not play a major role. Improvements in endothelial function, especially to exercising muscle beds and improvement in skeletal muscle oxidative capacity appear to be the major favorable adaptations to exercise training that result in improved exercise capacity.[285-287]

Patients on CSs after HT develop both metabolic bone disease with osteopenia and osteoporosis, along with skeletal muscle atrophy. These complications of therapy delay recovery and directly contribute to reduced physical function. Small controlled trials using resistance exercise training, often using simple techniques, have demonstrated restoration of BMD and prevention of skeletal muscle atrophy.[260, 288] In addition, resistance training has been shown to have a complementary effect with pharmacologic therapy with alendronate in restoring BMD.[261]

Rehabilitation and exercise training also are important issues after pediatric HT. These patients often have prolonged pre- and post-transplantation stays in intensive care units and many suffer muscle wasting due to pronged immobilization associated with ECMO runs and other MCS therapies. Despite the greater mobility with MCS devices before transplant, many children still have abnormal exercise and play capacities. Other factors that contribute to limited exercise capacity in the pediatric HT population include obesity and neurologic deficits, which may be multifactorial or result from strokes as a complication of MCS devices. There is limited literature on exercise and cardiac rehabilitation in the pediatric HT recipient. Although pediatric HT recipients may achieve near normal heart rates at peak exercise, other factors still limit their exercise capacity. Recent data have shown improved exercise performance after home exercise training,[289] but more work is needed to determine if the encouraging short-term results can be sustained.

Finally, exercise training may have other potential favorable effects on HT patients including preventing some of the side effects of immunosuppressive therapy and reducing cardiovascular risk factors such as insulin resistance, obesity, hypertension, and hyperlipidemia. There are no conclusive data to currently support the role of either aerobic or resistance exercise training in these important areas of post-transplantation care.

Recommendations for Exercise and Physical Rehabilitation After Heart Transplantation[279, 280, 282-289]:

Class I:

1. The routine use of cardiac rehabilitation with performance of aerobic exercise training is recommended after HT. The short-term benefits of this approach include improvement in exercise capacity and possible modification of cardiovascular risk factors such as obesity, hypertension, and glucose intolerance. There is currently no information on potential long-term benefits.

   Level of Evidence: B.

2. Resistance exercise is also strongly encouraged in HT recipients to restore BMD and prevent the adverse effects of CS and CNI therapy on skeletal muscle. Resistance exercise should be additive to other therapies for bone mineral loss and muscle atrophy.

   Level of Evidence: B.

Class IIa:

1. Exercise should be encouraged after pediatric HT, although no data on the long-term benefits exist. Exercise has been shown to produce short-term improvements in functional capacity and perhaps to decrease obesity-related morbidity. Specific exercise programs should be tailored to the specific needs and co-morbidities of the individual HT recipient.

   Level of Evidence: C.

Topic 12: Management of Intercurrent Surgery in Heart Transplant Recipients

Recipients of HT undergoing intercurrent surgical procedures should pose little additional management hazard ***provided*** certain potential complications directly related to immunosuppressive therapy and the physiology of the denervated heart are recognized and avoided (Table 3).

There is a potential for poor wound healing in patients having major surgery while taking PSIs and the benefit/risk ratio of continuing versus stopping these agents should be discussed with the transplant center; there are no parenteral preparations of SRL or EVL. The CSs should be continued at the usual dose, but additional "stress CS doses" should be considered if the patient is undergoing a major operation or CS daily doses > 10mg in the preceding 3 months. A typical stress CS dosing regimen includes 25 to 50 mg IV hydrocortisone at anesthesia induction, followed by IV hydrocortisone 25 to 50 mg 3 times daily for up to 72 hours. The usual pre-operative dose of oral CSs should be resumed when IV hydrocortisone is stopped.

Table 3 Conversions of Oral to Intravenous Doses of Immunosuppressive Drugs

Cyclosporine	One-third of oral daily dose as either a continuous infusion over 24 hours, or divided into two 6 hourly infusions twice daily
Tacrolimus	One-fifth of the oral daily dose as a continuous infusion over 24 hours
Mycophenolate mofetil	Same as oral dose
Azathioprine	Same as oral dose

Recommendations on the Management of Intercurrent Surgery in Heart Transplant Recipients[290]:

(See Table 3)

Class I:

1. HT recipients requiring intercurrent surgical procedures should have full pre-operative assessment in collaboration with the HT team particularly in preparation for major procedures requiring general or regional anesthesia.

   Level of Evidence: C.

2. For many surgical procedures, prophylactic antibiotic administration is now the norm. Protocols may need modification in HT recipients; aminoglycoside antibiotics and erythromycin are best avoided because of the risk of worsening renal dysfunction when used in combination with CYA or TAC.

   Level of Evidence: C.

3. When needed, blood products used in HT recipients should be leukocyte poor. ABO-incompatible infant HT recipients require specialized blood products and must be discussed with the transplant center.

   Level of Evidence: C.

4. Anesthesia can be safely induced provided that there is clear understanding that the HT is denervated. Resting heart rate is usually higher in HT recipients. Although most HT have a resting heart rate of approximately 90 bpm, some have resting sinus rates as high as 130 bpm which do not require treatment. It must be remembered that a relative, symptomatic, bradycardia that requires treatment will not respond to atropine. Isoproterenol infusion and pacing are the usual modes of management of HT bradyarrhythmias. Although uncommon, the

likeliest sustained atrial arrhythmia is atrial flutter. Likewise, the denervated heart is super-sensitive to adenosine and the use of standard doses to treat atrial tachyarrhythmias may result in prolonged asystole. Amiodarone is recommended as the drug of choice for atrial tachyarrhythmias in HT recipients.

Level of Evidence: C.

5. Care with fluid balance is important as decreased intravascular volume will exacerbate renal dysfunction, and fluid excess may not be well tolerated by HT recipients. For major surgery, central venous pressure (CVP) monitoring may be necessary.

   Level of Evidence: C.

6. Immunosuppression should not be discontinued or omitted without discussion with the HT team. However, it may be prudent to omit the dose of CNI on the morning of surgery to avoid potentiating the detrimental effect of dehydration on renal function. Thereafter, immunosuppression should be continued as normal. If medications cannot be given orally, CYA should be given IV (often as a 6-hour infusion every 12 hours or as a continuous infusion over 24 hours) at one-third of the daily oral dose; TAC can be given IV at a dose one-fifth of the total daily oral dose over 24 hours; AZA should be given IV once daily at the same dose as that taken orally; MMF can be given IV at the same dose taken orally.

   Level of Evidence: C.

Topic 13: Return to Work or School and Occupational Restrictions After Heart Transplantation

Three prospective studies have shown return to work rates at 1 year after HT of 26%, 69.4%, and 90%. However, the last study only included 10 patients. Moreover, the first study defined return to work as "having a paid job", while the latter 2 used a broader definition, including also students, retired patients, and housekeepers. Three additional cross-sectional studies yielded similar results, with approximately 34% (considering those with a paid job only) to 48% of the patients (including students, homeworkers, and retired patients as well) working at 2 to 3 years after HT. Because the studies summarized above were mostly from North America, return to work rates for European, Asian, or Australian HT recipients is unknown. The majority of patients returned to work within the first 6 months after HT. Factors consistently associated with return to work in solid organ transplant recipients are: younger age at the time of transplantation, a higher educational level, a better perceived functional ability, having worked before transplant or shorter period off work before transplantation, and no loss of insurance or disability income when returning to work. It is unclear whether those with a better perceived physical quality of life are more likely to go to work, or whether return to work results in a better quality of life. Few studies have tested the effect of formal vocational programs on return to work rates after HT, yet, 1 study showed that centers with formal vocational programs stimulating all patients to return to work after HT had higher employment rates compared to those without such programs. Furthermore, no studies have been published on which occupational restrictions are appropriate for HT recipients. Other than avoidance of exposure to infectious agents, there seem to be few obvious occupational restrictions for HT recipients. In many countries, additional factors affecting return to work are the ability to find suitable work and maintain adequate health coverage. Many HT recipients able to return to work are covertly discriminated against in the workplace due to employer fears of increased healthcare costs and/or the potential for job absenteeism due to ongoing health issues. Additionally, many HT patients receive government or company-sponsored healthcare benefits due to their ongoing disability. If no longer considered disabled, healthcare benefits stop.

Return to School:

The general consensus is to encourage children to return to school early after HT. Typically, children will return to school approximately 2 months after HT, although for younger children return to day care should also be encouraged as many parents must return to work. However, avoidance of day care during times of seasonal viral illnesses outbreaks such as influenza or respiratory syncytial virus infections can be helpful early after HT.

Recommendations on Return to Work or School and Occupational Restrictions After Heart Transplantation[291-293]:

Class IIa:

1. Healthcare providers should know that return to work for HT recipients is possible, and not passively support the sick role of patients.

   Level of Evidence: C.

2. Return to work should be discussed before HT as the goal of post-operative rehabilitation, and not as an exception.

   Level of Evidence: C.

3. Patients should be encouraged to maintain their job as long as possible before HT, as this facilitates return to work after HT.

   Level of Evidence: C.

4. Short- and long-term goals for returning to work should be discussed as part of the discharge planning after HT.

   Level of Evidence: C.

5. An employment specialist (e.g., a social worker) should be appointed who can set up a proactive employment atmosphere and facilitate the return to work process after HT.

   Level of Evidence: C.

6. This employment specialist should: (1) perform a formal assessment of the patient's educational backgrounds, skills, beliefs, functional and physical limitations and former work experiences; (2) formulate a career plan with the patients that may help the patient to enter or re-join the work force or acquire further vocational training; (3) have knowledge of the job market and collaborate with the HT team in learning which physical limitations of the patients must be taken into account; (4) educate future employers about HT and share insights about an individual patient's abilities and restrictions in view of post-operative rehabilitation.

   Level of Evidence: C.

Topic 14: Return to Operating a Vehicle After Heart Transplantation

In addition to the usual post-sternotomy precautions, HT recipients have unique issues that must be addressed before allowing return to driving a motor vehicle. Although common driving laws have geographic variations, restrictions related to the risk of syncope are ubiquitous. Drivers that have had syncope must be free of recurrence for a specified period of time, usually 6 months. In addition, it is often required that the cause of syncope be identified and treated before the permission to drive is issued. It is advisable that visual acuity be assessed in all HT recipients as vision may change in the post-operative period due to medications and other factors. Gate stability, tremor, and other neurologic complications should be assessed before release for driving. Symptomatic bradycardia after HT is uncommon, but if present, implantation of a permanent pacemaker may be indicated before resumption of driving. Finally, the absence of hypoglycemic events should be ascertained. Resumption of occupational driving requires successful completion of the requirements mandated by the specific country and it may be more difficult. Patients wishing to pilot an aircraft require a high level of scrutiny, but may be able to return to flying in some countries. The risk of sudden death when a HT recipient develops CAV explains the reluctance of regulatory agencies to grant HT recipients the permission to fly an aircraft.

Recommendations for the Operation of a Vehicle After Heart Transplantation

Class I:

1. Assessment and discussion of the ability to drive a motor vehicle should be included in the early follow-up of HT recipients.

   Level of Evidence: C

2. Gate stability, tremor, and other neurological abnormalities should be assessed before HT recipients obtain the permission to drive.

   Level of Evidence: C

3. If symptomatic bradycardia is present after HT, the implantation of a permanent pacemaker should be considered before driving is permissible.

   Level of Evidence: C

4. The absence of severe hypoglycemic events should be ascertained before HT recipients are permitted to drive.

   Level of Evidence: C

5. Occupational driving requires that HT recipients meet their country's requirements for occupational driving.

   Level of Evidence: C

6. A high level of scrutiny is required for HT recipients requesting to pilot an aircraft due to the risk of sudden death associated with CAV.

   Level of Evidence: C

Topic 15: Cardiac Retransplantation

Fourty to 60 repeat HTs have consistently been performed each year with a cumulative incidence in adults of 3%.[294] The major indications for repeat HT are CAV, primary graft failure (PGF), and acute rejection. Survival after retransplantation is lower than that after primary HT, with 1- and 5-year survival rates of 56% and 38%, respectively.[117] Survival after retransplantation for CAV is significantly greater than that for PGF or rejection and in highly selected individuals, is similar to that of primary HT. [117, 295] Risk factors for mortality after repeat HT include allograft failure < 6 months, reoperation for acute rejection, and HT center volume.[115, 296] Survival is significantly affected by the time interval between operations. One-year survival was only 50% when HTs occurred < 6 months apart, but rose to 75% when this interval was more

than 2 years.[115] Rates of infection and rejection are similar for primary and repeat HT. Post-operative management is similar to that after primary HT. The paucity of donors has raised ethical questions regarding the appropriateness of repeat HT,[297] but there is consensus that that appropriate candidates for retransplantation can be identified on the basis of the likelihood of successful outcomes.[118]

The expectation of retransplantation is widely held by pediatric recipients and their families. Because HT half-life is approximately 12.5 years, young recipients face death in their teenage and young-adult years without the prospect of retransplantation. Data on retransplantation from the Pediatric Heart Transplant Study (PHTS) database[298] and the United Network for Organ Sharing (UNOS)[299] demonstrated that 5-year patient survival after retransplantation was inferior to that after primary HT (53% vs. 60%). As in adults, retransplantation for PGF, rejection, or reoperation within the first 6 to 12 months after primary HT is associated with very poor outcomes compared to those of later retransplantation for CAV. Although not identical, ISHLT recommendations for retransplantation of pediatric HT recipients are similar to those issued by the American Heart Association (AHA).[300]

Recommendations for Cardiac Retransplantation[294, 296, 298]:

Class I:

1. Retransplantation is indicated in children with at least moderate systolic heart allograft dysfunction and/or severe diastolic dysfunction and at least moderate CAV.

   Level of Evidence: B.

Class IIa:

1. It is reasonable to consider listing for retransplantation those adult HT recipients who develop severe CAV not amenable to medical or surgical therapy and symptoms of heart failure or ischemia.

   Level of Evidence: C.

2. It is reasonable to consider listing for retransplantation those HT recipients with heart allograft dysfunction and symptomatic HF occurring in the absence of acute rejection.

   Level of Evidence: C.

3. It is reasonable to consider retransplantation in children with normal heart allograft function and severe CAV.

   Level of Evidence: B.

Class IIb:

1. Patients with severe CAV not amenable to medical or surgical therapy with asymptomatic moderate to severe LV dysfunction may be considered for retransplantation.

   Level of Evidence: C.

Class III:

1. Adult and pediatric HT recipients with heart allograft failure due to acute rejection or occurring less than 6 months after the first HT and complicated by hemodynamic compromise are inappropriate candidates for retransplantation.

   Level of Evidence: C.

Topic 16: Endocarditis Prophylaxis After Heart Transplantation

Endocarditis after HT is uncommon, but when it does occur the mortality has been reported to be as high as 80%.[301] The major pathogens are *Staphylococcus aureus* and *Aspergillus fumigatus*. Factors associated with *S. aureus* infection include the use of hemodialysis catheters, cellulitis, and a contaminated donor organ. Patients with *A. fumigatus* have been reported to suffer antecedent CMV viremia and to frequently have disseminated fungal infection, including endophthalmitis.[301]

The HT recipients who develop valvular heart disease are considered to be at the highest risk for endocarditis. The infection typically involves the inlet valves (mitral valve and tricuspid value) or the suture line above the aortic valve. Early post-operative infection appears more common than later infection. Although no formal studies have been carried out, it seems likely that that the need for endocarditis prophylaxis is reduced after the initial post-operative period if valvular dysfunction is absent.

The AHA guidelines[302] state that there are insufficient data to support specific recommendations for HT recipients. However, because these patients are at risk of acquired valvular dysfunction, and the outcome of endocarditis in HT recipients is poor, the use of antibiotic prophylaxis for dental procedures in HT recipients is considered reasonable in the AHA guidelines.

Recommendations on Endocarditis Prophylaxis in Heart Transplant Recipients:

Class IIa:

1. There are insufficient data to support specific recommendations for endocarditis prophylaxis in HT recipients. However, these patients are at risk of acquired

valvular dysfunction and the outcome of endocarditis is so poor in HT recipients that the use of antibiotic prophylaxis for dental procedures is considered reasonable in patients with valvulopathies.

Level of Evidence: C.

Topic 17: Frequency of Routine Tests and Clinic Visits in Heart Transplant Recipients

No studies or consensus statement exist on the optimal frequency of routine tests or clinic visits. The following recommendations might be used as a starting point to reach consensus on the most appropriate follow-up schedule for HT recipients.

Some of the recommendations below are supported by the guidelines issued by the American Society of Transplantation (AST).[303]

Recommendation on the Frequency of Routine Tests and Clinic Visits in Heart Transplant Recipients[303]:

Class IIa:

1. Lifelong follow-up by the transplant center is recommended for HT recipients due to: (1) the possibility of acute and/or chronic rejection; (2) the chronic use, toxicity and drug interactions of immunosuppressants and the associated risks for infection and malignancy; and (3) comorbidities requiring specialized monitoring and management.

   Level of Evidence: C.

2. Follow-up for HT recipients should be provided by a multidisciplinary team, including surgeons, cardiologists, nurses, psychologists, social workers, dieticians, physiotherapists, among many others. Patients and care givers should recognize that HT requires a life-long commitment to medical care.

   Level of Evidence: C.

3. The frequency of follow-up visits for HT recipients will depend on the time since HT and the post-operative clinical course.

   Level of Evidence: C.

4. In case of an uneventful recovery, follow-up visits are best scheduled every 7 to 10 days during the first month after HT, then every 14 days during the second month, monthly during the first year, and every 3 to 6 months thereafter.

   Level of Evidence: C.

5. The frequency of follow-up should be increased if complications occur, particularly in patients with challenging medical or psychosocial conditions.

   Level of Evidence: C.

6. Ancillary services including home care nursing, cardiac rehabilitation, psychological support, nutritional planning, or patient support groups may also be used as resources in the follow-up of HT recipients, with the understanding that providers of community healthcare services must communicate with the clinicians at the transplant center to ensure that the care delivered complies with the HT center's standards.

   Level of Evidence: C.

7. Local health professionals should inform the transplant center in the case of the following events: (1) hospitalization for any reason; (2) change in medication including the addition of any antibiotic, antifungal, or antiviral therapy for confirmed or presumed infection; (3) hypotension or unexplained drop in systolic blood pressure ≥ 20 mmHg from baseline; (4) increase in resting heart rate > 10 bpm over baseline; (5) fever ≥ 101ºF (38°C) or any unexplained fever ≥ 100.5ºF (38°C) for ≥ 48 hours; (6) ≥ 2 lb weight gain in 1 week (i.e., 900 g or more); (7) unexplained weight loss of > 5 lb (i.e., 2.3 kg); (7) elective surgery; (8) increased shortness of breath; (9) pneumonia or any respiratory infection; (10) syncope; (11) chest pain other than musculoskeletal symptoms; (12) decline > 10% in FEV_1 (forced expiratory volume in 1 sec); (13) abdominal pain; (14) nausea, vomiting or diarrhea; (15) cerebral vascular event, seizure or mental status changes.

   Level of Evidence: C.

Class I:

1. In addition to routine outpatient follow-up visits HT recipients should have more prolonged visits every 1 to 2 years for more detailed clinical assessment.

   Level of Evidence: B.

2. The purpose of the follow-up visits is to monitor for rejection and screen for adverse events, and may include the following: (1) a complete physical examination; (2) review of the medication and changes to the medication based on the results of the examinations; (3) blood work; (4) echocardiogram; (5) coronary angiography and IVUS (every 1 to 2 years); (6) EMB as per the typical schedule outlined below; (7) additional education or and interaction with members of the multidisciplinary team.

An example of a typical biopsy schedule for the first year could be:

Biopsy 1, 2, 3, 4 and 5:	Weekly
Biopsy 6, 7 and 8:	Every 14 days
Biopsy 9 and 10:	Every 3 weeks
Biopsy 11, 12 and 13:	Every 4 weeks
Subsequent biopsies during the first year after HT:	Every 5 to 6 weeks

This recommendation is addressed in more detail in Task Force 2.

Level of Evidence: B.

3. In pediatric practice, far fewer biopsies are performed due to the need for general anesthesia in small children and the difficulties with venous access and bioptome manipulation in small hearts and vessels. There is no consensus on the frequency of biopsy in children. Some centers do no EMB at all, but instead use detailed echocardiographic assessment. Besides scheduled clinic appointments, the patients should be encouraged to contact the transplant center with questions, concerns, or unexpected symptoms.

   Level of Evidence: C.

Topic 18: Psychological Issues Particularly Related to Adherence to Medical Therapy in Heart Transplant Recipients

A substantial proportion of HT recipients are not adherent to the prescribed therapeutic regimen. A meta-analysis showed that yearly, of 100 cases, 14.5 are non-adherent to the immunosuppressive medication, 3.2 smoke, 4.9 report excess alcohol intake, 1.use illicit drugs, 8.5 miss scheduled appointments, 13.3 fail to have the prescribed diagnostic tests 28.1 do not follow the recommended diet, and 33.7 do not follow their exercise prescription, with an overall non-adherence rate of 17.8 cases per 100 patients per year. Furthermore, 75% of transplant recipients do not follow the recommended sun protection measures. Studies in pediatric HT recipients report even higher rates (46%) of non-adherence to the immunosuppressive regimen, especially during adolescence.

Evidence in solid organ transplant recipients shows that non-adherence to immunosuppression increases the risk for late acute rejections or graft loss. The reasons for non-adherence are usually multifactorial, including socioeconomic reasons (younger age, lack of social support, financial problems), psychological issues (depression, substance abuse), treatment-related factors (presence of distressing side effects, complexity of treatment regimen), and patient-related factors (insufficient knowledge, poor coping mechanisms, forgetfulness, busy lifestyle or wrong health beliefs). Authoritarian communication style, insufficient follow-up, and lack of health insurance add complexity to the issue of non-adherence. Limited evidence on adherence-enhancing interventions exists in the transplant literature, but evidence from other chronically ill populations shows that interventions should target all modifiable risk factors, both at the patient and healthcare system levels.

Recommendations on Psychological Issues After Heart Transplantation[304-310]:

Class IIa:

1. Adherence with the prescribed regimen should be routinely assessed at every HT outpatient clinic visit.

   Level of Evidence: C.

2. Since there is currently no gold standard for adherence assessment in HT recipients, it is recommended to combine methods in order to increase accuracy of assessment (e.g., a combination of self-report or parent report in the case of children, drug levels assessment, and clinical judgment).

   Level of Evidence: C.

3. Attention should be given not only to adherence to the immunosuppressive regimen, but to all other health recommendations appropriate for HT recipients.

   Level of Evidence: C.

4. Barriers to adherence should be discussed in an open, non-threatening way during visits with HT recipients.

   Level of Evidence: C.

5. Tailored interventions, in close collaboration with the HT recipient and his/her family, should be considered and their efficacy explored. Strategies that seem most effective include offering education repeatedly, reducing the complexity of the medication regimen, providing feedback on a patient's behavior, and combining strategies.

   Level of Evidence: C.

6. Strategies to enhance maturity and independence may be particularly helpful in the adolescent HT recipients.

   Level of Evidence: C.

7. Since adherence to medical recommendations is a complex issue, healthcare teams would benefit from training in measuring adherence, discussing its barriers, and implementing adherence-enhancing interventions for HT recipients.

   Level of Evidence: C.

8. Each HT center should closely collaborate with a specialized nurse or psychologist who can screen and follow all HT recipients at risk for non-adherence. Investing in specialized staff may result in better transplant outcomes in the long-term, although further studies testing the efficacy of adherence-enhancing interventions are warranted.

   Level of Evidence: C.

9. Depressive symptoms should be regularly evaluated during follow-up of HT recipients. This can best be done by user friendly, validated screening instruments. All patients with elevated scores should be referred to specialized treatment.

   Level of Evidence: C.

10. Each HT team should include a psychologist who is qualified to detect and treat depression. Multidisciplinary treatment teams are better prepared to address psychosocial risk factors for poor outcomes after HT.

    Level of Evidence: C.

Class I:

1. Serotonin re-uptake inhibitors, particularly citalopram, and new-generation anti-depressants (mirtazapine) may be the best choice for HT recipients as they have no significant impact on blood pressure, heart rate, rhythm, or conduction intervals.

   Level of Evidence: B.

2. Agents that interact with the metabolism of CYA and TAC via the CYP-450 system (e.g. fluvoxamine, nefazodone) should be avoided because they may alter CNI levels.

   Level of Evidence: B.

3. Tricyclic anti-depressants (e.g., imipramine, desipramine, amitriptyline, comipramine) are associated with cardiovascular toxicity (conduction delay, orthostatic hypotension, and anti-cholinergic effects) and may lower seizure thresholds and, therefore, their use should be restricted to HT recipients with severe depression refractory to other therapies. Monoamine oxidase inhibitors (MAOIs) should be avoided because of their hypotensive effects, interactions with anesthetic and pressor agents and need for dietary restrictions. Herbal medicines, such as St. John's wort (Hypericum iperforatum), can be harmful because it lowers CYA levels.

   Level of Evidence: B.

Topic 19: Management of the Transition from Pediatric to Adult Care After Heart Transplantation

Successful transition of pediatric HT recipients to adult care requires coordinated interdisciplinary planning by the pediatric and adult HT teams and the patient/family unit. A healthcare provider responsible for coordination of transition and a written plan created together with the young person and family may facilitate a successful transition to an adult care environment.

Critical milestones to be achieved by pediatric HT recipients before transition to adult care include: (1) an understanding of and ability to describe the original cause of their organ failure and need for HT. Initial education may have been primarily provided to their parents; repetition is necessary to ensure understanding of their condition; (2) awareness of the long- and short-term clinical implications of chronic immunosuppression (infection prevention, cancer surveillance, academic and vocational aspirations); (3) comprehension of the impact of HT status on sexuality and reproductive health (impact of pregnancy , effect of medications on fertility, any potential teratogenicity of medications, role of genetic counseling, and genetic risk of their disease recurrence in offspring, increased susceptibility to sexually transmitted disease); (4) demonstration of a sense of responsibility for their own healthcare (knowledge of medications, ability to prescription refills, adherence to medication and office visits schedules, ability to independently communicate with healthcare providers, recognition of symptoms and signs requiring immediate medical attention, understanding of health care coverage and eligibility requirements). Simultaneously healthcare providers should prepare parents for the transition by encouraging independence and self-responsibility in the child.

Adult practitioners should cultivate partnerships with their pediatric colleagues to gain insight into the care of adolescents, the impact of childhood chronic disease on development, and management of childhood causes of end-stage organ failure and congenital diseases. Ideal adult site resources also include a dedicated transfer liaison nurse coordinator, a social worker, and a reproductive specialist.

Recommendations on the Management of the Transition from Pediatric to Adult Care After Heart Transplantation[311-313]:

Class I:

1. Critical milestones to be achieved by pediatric HT recipients before transition to adult care include: (1) an understanding of and ability to describe the original cause of their organ failure and need for HT. Initial education may have been primarily provided to the parents of the HT recipient; repetition is necessary to ensure understanding of the clinical condition by the HT recipient; (2) awareness of the long- and short-term clinical implications of chronic immunosuppression (infection prevention, cancer surveillance, academic and vocational aspirations); (3) comprehension of the impact of HT status on sexuality and reproductive health (impact of pregnancy, effect of medications on fertility, any potential teratogenicity of medications, role of genetic counseling, and genetic risk of disease recurrence in offspring, increased susceptibility to sexually transmitted disease); (4) demonstration of a sense of responsibility for self care (knowledge of medications, ability to obtain prescription refills, adherence to medication and office visits schedules, ability to independently communicate with health providers, recognition of symptoms and signs requiring immediate medical attention, understanding of health care coverage and eligibility requirements).

   Level of Evidence: C.

2. Healthcare providers should simultaneously prepare the parents for the transition from pediatric to adult care by encouraging independence and self-responsibility in the child.

   Level of Evidence: C.

3. Adult practitioners should cultivate partnerships with their pediatric colleagues to gain insight into the care of adolescents, the impact of childhood chronic disease on development, and management of childhood causes of end-stage organ failure and congenital diseases. Ideal adult site resources also include a dedicated transfer liaison nurse coordinator, a social worker and a reproductive specialist.

   Level of Evidence: C.

Topic 20: Principles of Shared Care After Heart Transplantation

Optimal care of the HT patient requires effective communication between the HT team and the referring physicians, especially for patients residing far from the transplant center and for children whose care involves immunizations, treatment of common acute infections, developmental issues, growth, development and possibly behavioral concerns. The HT team and referring physicians should coordinate their roles in a manner that is clearly recognized by the HT recipient.

Pre-transplant Period

Referral for HT should be based on up-to-date criteria for necessity and eligibility. After referral, the HT team and referring physician should decide jointly whether the patient should be evaluated as an inpatient or outpatient. While the patient is on the waiting list, decisions affecting cardiovascular care are the responsibility of the HT team, but the referring physician may have a key role in monitoring the patient's condition and implementing therapeutic decisions.

Post-transplant Period

After HT recipient discharge, the HT team is responsible for rejection surveillance and patient management during hospitalization. and communication with the referring physicians regarding cardiovascular management , specific interactions between drugs prescribed by the HT team and those that may be prescribed to treat ailments managed by the local physician In the case of pediatric patients, immunization schedules should be established by the HT team and communicated to the primary care physician. Conversely, the HT team should rely on referring physicians for information regarding medical interventions and changes in the patient's clinical condition.

Recommendations on the Principles of Shared Care of Heart Transplant Recipients:

Class I:

1. The HT team should ensure that other involved physicians know telephone numbers and electronic mail addresses of the HT team to enable contact at all times and guarantee prompt responses to referring physicians' queries.

   Level of Evidence: C.

2. It is helpful for physicians outside the HT team to receive the patient's plan for scheduled HT office visits at the transplant center.

   Level of Evidence: C.

3. Formal procedures should be instituted to regularly inform referring physician of clinical results and medical regimens.

   Level of Evidence: C.

ABBREVIATIONS

ACEI = angiotensin converting enzyme inhibitors
ADA = American Diabetes Association
AHA = American Heart Association
ARB = angiotensin receptor blocker
ARF = acute renal failure
AST = American Society of Transplantation
ATG = anti-thymocyte globulin
AZA = azathioprine
BMD = bone mineral density
BMI = body-mass index
CAD = coronary artery disease
CAV = cardiac allograft vasculopathy
CFR = coronary flow reserve
CKD = Chronic kidney disease
CMV = cytomegalovirus
CNI = calcineurin inhibitor
CNS = central nervous system
CPB = cardiopulmonary bypass
CrCL = creatinine clearance
CS = corticosteroid
CT = computerized tomography
CTRD = Cardiac Transplant Research Database
CVP = central venous pressure
CYA = cyclosporine
CYP = cytochrome P-450 enzyme system
DEXA = Dual-energy X-ray absorptiometry
DSE = dobutamine stress echocardiography
EBV = Epstein-Barr virus
ECMO = extracorporeal membrane oxygenation
EC-MPS = enteric-coated mycophenolate sodium
EMB = endomyocardial biopsy
FEV_1 = forced expiratory volume in 1 second
FSGS = focal segmental glomerulosclerosis
GFR = glomerular filtration rate
GI = gastrointestinal
HbA1c = glycosylated hemoglobin
HD = hemodialysis
HF = heart failure
Hgb = hemoglobin
HLA = human leukocyte antigen
HPV = human papillomavirus
HSV = herpes simplex virus
HT = heart transplant
ICU = intensive care unit
ISHLT = International Society of Heart and Lung Transplantation
IUD = Intrauterine devices
IVUS = intravascular ultrasound
LV = left ventricle
MAOI = monoamine oxidase inhibitors
MDRD = Modification of Diet in Renal Disease
MMF = mycophenolate mofetil
MPA = mycophenolic acid
mTOR = mammalian target of rapamycin
NKF-KDOQI = National Kidney Foundation's Kidney Disease Outcomes Quality Initiative
NPV = negative predictive value
NYHA = New York Heart Association
PAP = Papanicolau test
PCI = percutaneous coronary intervention
PCR = polymerase chain reaction
PD = peritoneal dialysis
PGF = primary graft failure
PHTS = Pediatric Heart Transplant Study
PRA = panel reactive antibody
PRES = posterior reversible encephalopathy syndrome
PSA = prostate-specific antigent
PSI = proliferation signal inhibitor
PTLD = post-transplant lymphoproliferative disorder
QCA = quantitative coronary angiography
RI = reperfusion injury
RV = right ventricle
sCr = serum creatinine
SRL = sirolimus
SRTR = Scientific Registry of Transplant Recipients
STI = sexually transmitted infection
TAC = tacrolimus
UNOS = United Network for Organ Sharing
V_E = ventilatory equivalent
VO_2 = peak oxygen consumption
VCO_2 = carbon dioxide production

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