Pediatric Transplant Patients and Their Medical Conditions/Therapies: Implications for Perioperative Management

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Transplantation in pediatric patients has become a common occurrence. Each year more than 2000 children receive solid organ transplants in the United States and this number is expected to increase in the future (UNOS database annual report 2001). Post transplant children may present for anesthesia and surgeries that are routine in pediatric patients (myringotomy with tubes, tonsillectomies, strabismus surgery, inguinal hernia repair) but have special implications in these patients. In this discussion we will review the common solid organ transplants that are being performed in pediatric patients including the indications for transplantation, currently administered immunosuppression agents and the special anesthetic considerations in patients with transplanted organs.

Solid Organ Transplants

Solid organ transplants in pediatric patients include heart, heart/lung, lung, liver, and kidney. The indications for heart transplantation are severe congenital malformations, such as hypoplastic left heart syndrome (which is usually performed in the neonatal period) or children with end stage cardiomyopathy who are usually older.[1,2] Occasionally the indications will include myocardial tumors but this is a rare event. The indications for heart/lung transplants are Eisenmenger's syndrome, congenital defects with pulmonary vascular disease, and complex congenital heart disease with inadequate pulmonary vessels that cannot be corrected with conventional surgeries. As far as lung transplants, the indications are primary pulmonary hypertension, pulmonary fibrosis, and possibly the most common being cystic fibrosis. Liver transplant indications include biliary atresia (a congenital abnormality) and metabolic diseases such as $alpha_1$ antitrypsin deficiency. Occasionally liver transplants are also done for patients with liver tumors. And finally kidney transplants (the most common transplant in children) are indicated in chronic renal failure patients of which there may be a myriad of underlying disorders, one of the more common ones being polycystic kidneys.

Table 1

Number of US transplants by recipient age: 1996-March, 2001[3]

	Recipient age (years)			
Organ (number of transplants)	**<1**	**1-5**	**6-10**	**11-17**
Heart	393	322	210	470
Heart-lung	5	16	6	13
Lung	30	27	54	174
Kidney	25	656	738	2149
Kidney-pancreas	3	6	2	2
Pancreas	10	14	5	10
Liver	851	995	433	618
Intestine	46	126	33	25

A child who presents with a transplanted organ for surgery unrelated to their transplant needs special considerations. In many respects, the perioperative management of a child who has undergone a successful organ transplant is similar to the standard practice for any child. It is important to be cognizant of specific potential problems related to immunosuppression therapy, risk of infection and potential for rejection.[4,5]

Rejection is a main cause of late mortality in children with organ transplants although a transplant in the neonatal period has been associated with a lesser risk of infection and rejection.[4,5,6,7] Rejection may present with progressive deterioration of organ function or with minimal symptoms from the transplanted organ and present with nonspecific symptoms such as poor appetite, irritability or fatigue. It has been shown that patients who undergo surgery during a period of rejection may have a higher morbidity.[4]

Pharmacological Considerations in Pediatric Transplant Recipients

Immunosuppressive Drugs

Immunosuppression is a key part of transplant protocols, but depending on the organ transplanted the immunosuppressive drugs will vary. All protocols include some period of steroid administration but the dose and duration of therapy is unique for the particular organ transplanted.

All transplant patients who come for surgical procedures will be on some antirejection protocol. It is important for anesthesiologists to know how these drugs interact with our anesthetic agents and also what side effects immunosuppressive drugs may exhibit. Therefore, a brief review of the most common drugs used for immunosuppression follows.

Calcineurin Inhibitors

Cyclosporine (CSA) selectively activates suppressor T cells while inhibiting B cell and cytotoxic T cell proliferation.[8] CSA interferes with the T cell receptor activated signal transduction pathology by binding calcineurin and inhibiting it's ability to induce genes encoding numerous cytokines (eg. interleukin, tumor necrosis factor and granulyte stimulating factor.[9] Adverse effects of CSA are nephrotoxicity, hepatotoxicity and neurotoxicity. These toxicities are largely dose related and can be reduced by monitoring blood levels[10] and minimizing the dose of CSA through the use of multiple drug immunosuppressive regimens.[10,11]

Nephrotoxicity is dose related, partially reversible and the most frequent and important injury. Hyperkalemic renal tubular acidosis can be treated with dose reduction or elimination of the drug altogether once a reduction in glomerular filtration rate or a serum creatinine over 2 mg/dl occurs.[10,11,12,13] Specific treatment for hyperkalemia is fludrocortisone acetate or kayexalate. It is very important that renal function is checked prior to administering anesthesia because if renal function is impaired this will prolong drugs that are excreted by renal clearance.

Cyclosporine induced hypertension is thought to be caused by renal vasospasm.[14] Nearly 75% of cardiac posttransplant recipients develop mild to moderate hypertension as a result of cyclosporine therapy.[15] In management of the hypertension, the patient may be treated with nifedipine, diltiazem or an angiotensin converting enzyme inhibitor. In cardiac transplant patients nifedipine may not be well tolerated because of it's prominent vasodilatory effects.

It is known, however, that calcium channel blockers increase blood levels of cyclosporine due to cytochrome P-450 inhibition. Beta blockers for treatment of hypertension are usually avoided in cardiac transplants since a resting level of catecholamines is necessary to maintain normal cardiac function.[16]

Hepatic toxicity consists of asymptomatic mild reversible elevations in bilirubin and occasionally transaminases suggesting cholestasis.[17] Central nervous system neurotoxicity can manifest as headache, paresthesias, tremor, confusion, flushing and seizures and may be present in half of the patients.[11,18,19,20]

Other side effects include hirsuitism, hyperlipidemia, gynecomastia, gingival hyperplasia, lymphoproliferative and infectious disorders and depression.[10,11,13] Bone marrow toxicity may manifest as leukopenia, anemia and thrombocytopenia.

Another alternatively used calcineurin inhibitor is tacrolimus (FK506). It inhibits T cell lymphocyte proliferation but is 100 times more potent than CSA.

It's use is for first line immunosuppression in liver transplants and it may eliminate long term steroid use in these pediatric patients. It may also be exchanged for CSA in kidney transplant patients undergoing rejection.

In heart transplants it may be used as a first line immunosuppressive instead of CSA and may allow the elimination of azathioprine and steroids from the maintenance regimen. It also seems effective in children who exhibit poor control of a CSA based triple immunosuppression protocol with rejection episodes.[21,22] It is used as first line immunosuppression in cardiac retransplant patients and those patients who have side effects from CSA therapy. However, there must be a 12-48 hour window from stopping CSA to starting tacrolimus. There have been reports of decreased hypertension (4% versus 70%) and no hursitism or gingival hyperplasia as compared to CSA. However, nephrotoxicity is seen, as well as pancreatitis with glucose intolerance in 22-47% of patients. Alopecia, bone marrow suppression, increased lymphoproliferative disease and infectious diseases are other side effects.

Hypertrophic obstructive cardiomyopathy associated with the use of tacrolimus is a rare complication of liver transplantation seen almost exclusively in pediatric patients. Conversion to sirolimus is associated with a reduction in the cardiomyopathy while still providing effective immunosuppression.[23]

Drug Interactions

Drugs that increase tacrolimus (FK506) and CSA levels are verapamil, diltiazem (not nifedipine) (via cyclochrome P450 inhibition), ketoconazole, fluconazole, itraconazole, erythromycin, clarithromycin and azithromycin, imipenem, ciprofloxacin, corticosteroids and metoclopramide. Drugs with synergistic nephrotoxicity are gentamycin, tobramycin, amphotericin B, vancomycin, trimethoprim/sulfamethoxazole, cimetidine, ranitidine, ketoconazole, and ganciclovir. Drugs that decrease the levels of both tacrolimus (FK506) and CSA are anticonvulsants and rifampin via cyctochrome 450 induction.

Antimetabolites

Antinucleotide antimetabolites excrete their immunosuppressive effects by inhibiting lymphocyte proliferation and antibody production. Azathioprine inhibits both DNA and RNA synthesis and thus all immune functions requiring cell proliferation.[8] The main side effects of azathioprine are bone marrow depression and hepatotoxicity. Angiotensin converting enzyme inhibitors such as captopril (which may be used to treat cyclosporine induced hypertension) will increase the incidence of leukopenia.

Mycophenolate (Cellept®) may be used instead of azathioprine for first line immunosuppression. An advantage is that there is no interaction with cyclosporine and prednisone, however, it does have side effects that include nephrotoxicity, hepatotoxicity, and bone marrow depression. As mentioned earlier, mycophenolate may be used during rejection periods in which it is substituted for azathioprine. Hemorrhagic gastritis and leukopenia are increased with the concurrent administration of ganciclovir and acyclovir which are both used to treat CMV infections.

Interleukin-I Inhibitors

Steroids are used in all transplantation patients for a period of time. The most common preparations are either prednisone, prednisolone, or methylprednisolone. When the patient is switched from an intravenous form to an oral form of steroids the correct dosage must be maintained. Prednisone has the advantage that it only needs to be given once a day. They may also be used as "pulse therapy" during rejection episodes.

Induction Immunotherapy

OKT3 was originally used in kidney transplants but has been replaced by other agents. Intraoperative administration caused anaphylaxis that presented as hypotension, bradycardia, pulmonary edema and even cardiac arrest. It is important that when this drug is given intraoperatively to avoid fluid overload and high concentrations of volatile agents. If an anaphylactic reaction does occur treatment includes vasopressors and inotropes for bradycardia and hypotension; fluid restriction, PEEP and diuretics for pulmonary edema and bronchodilators for wheezing. Seizures can be treated with benzodiazipines but many times phenytoin is given prophylactically to prevent seizures in patients in which OKT3 is administered.

Antithymocyte antibodies are added to now more commonly induction regimens for heart transplants at large centers. Currently antithymocyte globulin (Thymoglobulin®) is administered on 3-5 consecutive days. It is also used for 7-10 days for those patients with hemodynamically compromised or persistent rejection. Adverse reactions include fever, chills, rash, pain and pulmonary edema/bronchospasm. Anaphylaxis can occur at any time during the course of treatment but skin tests are not currently performed at our center prior to the administration of the drug. Pretreatment with acetaminophen, diphenhydramine and steroids can decrease side effects. Another preparation, antilymphocytic globulin equine (Atgam®), can be used but has a higher incidence of serum sickness.

TOR Inhibitors

Sirolimus (Rapamune®) is neither a calcineurin inhibitor like CSA nor an antimetabolite like azathioprine. It has a distinct cellular target referred to as the mammalian target of rapamycin or mTOR. It inhibits cell cycle progression but is specific, reversible and noncytotoxic.

In patients with renal dysfunction due to CSA or tacrolimus, sirolimus can be added to decrease their dose and renal effects. It may also be used if a patient develops posttransplant lymphoproliferative disease. All immunosuppressive drugs must be stopped during treatment of these neoplastic processes and after treatment sirolimus may be started as sole immunosuppressive therapy.

In patients that develop coronary vasculopathy, sirolimus may be added along with a lipid lowering agent such as pravastatin sodium (Pravachol®) or atovastatin calcium (Lipitor®) to prevent progression. In adult cardiac transplants addition of sirolimus not only prevented progression but also caused regression of the vasculopathy.[24]

Drugs that increase sirolimus levels include nicardipine, verapamil, diltiazem, cisapride, metoclopramide, cimetidine, and fluconazole. Drugs that decrease sirolimus levels are carbamezpine, phenobarbital, phenytoin and rifampin.

IL-2 Receptor Antagonists

Basiliximab (Simulect®) is a chimeric monoclonal antibody produced by recombinant DNA technology. Daclizumab (Zenapax®) is a humanized IgG monoclonal antibody. Both can be used for induction therapy post transplant and are given close to the time of the initial transplant.

Table 2 shows the side effects of commonly used immunosuppressive drugs that have a direct impact on anesthetic and perioperative management.

Table 2

	Ster	Aza	CyA	Tacr
Blood				
Anemia	-	+	-	-
Thrombocytopenia	-	+	-	-
Leucopenia	-	+	-	-
Cardiovascular				
Hypertension	+	-	++	+
Endocrine				
Diabetes	++	-	+	++
Neurotoxicity	+	-	+	+
Renal insufficiency	-	-	+	++
Others				
Anaphylaxis	-	-	-	-
Fever	-	-	-	-

Ster, steroids; Aza, azathioprine; CyA, cyclosporine; Tacr, tacrolimus (FK506).[3]

Anesthetic Agents

Immunosuppressive drugs may modify the pharmacological effects of many drugs used in anesthesia. Cyclosporine has been noted to potentiate the effect of barbituates, fentanyl and muscle relaxants particularly vecuronium and atracurium.[25] Thus a smaller dose of nondepolarizing muscle relaxants may be needed and recovery time may be prolonged. Azathioprine has been reported to antagonize competitive neuromuscular blocking drugs by its phosphodiesterase inhibiting properties and therefore larger doses of nondepolarizing blocking agents may be needed.[15] However it may prolong the effect of succinylcholine.

Succinylcholine is contraindicated in patients with renal impairment and hyperkalemia but otherwise can be used in children. Atracurium or cisatracurium are particularly suitable in patients with renal or hepatic impairment as they are metabolized by Hoffmann reaction. Mivacurium is useful for short procedures or as an infusion with excellent recovery.

Preoperative Assessment

Preoperative assessment must focus on the transplanted organs function, the state of immunosuppression, presence of rejection or infection and the function of other organs. Renal function and hemotologic status must be assessed in all transplant recipients due to the possibility of compromise from immunosppression.

The presence of an infection must be ruled out and perioperative antibiotic prophylaxis should be used the same as in nontransplant patients. The use of aseptic techniques with gowns, gloves and handwashing are particularly important in these immune suppressed patients. Intravenous and monitoring lines should be inserted with specific indications and removed as soon as they are no longer necessary for patient care.

The incidence of post transplant lymphoproliferative disease in tonsils after transplantation is low but may cause airway obstruction and should be evaluated in allograft recipients.[26]

Immunosuppressives must be maintained and the dose should not be altered perioperatively unless the route needs to be changed from oral to intravenous. To maintain therapeutic blood levels oral cyclosporine or tacrolimus must be administered 4-7 hours before surgery. Remember hemodilution or bleeding during the operation can result in decreased blood levels of cyclosporine or tacrolimus so their blood levels must be carefully monitored. The intravenous dose of cyclosporine is one third of the oral dose. Oral and intravenous dose of azathioprine are approximately equivalent, as is the oral dose of prednisone and the intravenous dose of methylprednisolone. Steroid "stress coverage" is not necessary unless the transplant recipient has been recently withdrawn from them.[27,28]

Another important aspect in care of these patients is emotional care. These children have been through many medical procedures and contacts with physicians and hospitals. Therefore we must address their emotional needs and the emotional needs of their parents when they come for surgical procedures. Oral midazolam syrup is effective in producing sedation and anxiolysis in small doses 0.25 mg/kg.[29] Also children with transplanted organs should not be allowed to become volume depleted with excessive NPO times. Local anesthetic cream can assist with IV insertion but many children will have long-term central venous catheters that can be used.

Abdominal complications including visceral perforation and death are a common risk of organ transplantation. The immunosuppressed patient doesn't present with typical signs of sepsis, thus the threshold for surgical intervention is lower in these cases.[30]

Intraoperative Management

Any anesthetic technique can be used in these children as long as their underlying pathophysiology is considered. Orotracheal intubation is preferred over nasal intubation to avoid potential infection caused by nasal flora.[31] If an epidural or spinal technique is planned coagulation should be normal. Perioperative monitoring should be determined by type of surgery and anesthesia planned and inserted under strict aseptic technique.

Postoperative Care

Analgesias such as acetaminophen can be used after taking into account the individual features of the child. The use of nonsteroidal antiinflammatory drugs should be avoided becasue of the increased risk of nephrotoxicity when cyclosporine or tacrolimus are coadministered. Epidural block, wound infiltration or peripheral nerve blocks can be useful for postoperative pain management, with no evidence of increased risk of central blockade if the child is on long term steroids.[32]

Posttonsillectomy surgical edema may contribute to airway obstruction and require postoperative intubation.[26] Patients can have surgery in ambulatory surgery centers for minor procedures as long as they are medically stable.

Special Considerations in Patients with a Transplanted Heart

Patients with a transplanted heart have numerous areas of abnormalities that make them special anesthetic challenges. Denervation, coronary vasculopathy, and rejection are all important aspects to consider before anesthesia is administered.

Denervation

Denervation is a very important problem for the anesthesiologist. Responses that are normally mediated via the autonomic nervous system are absent. These responses may include vagal slowing and the baroreceptive response to blood pressure changes. Changes in heart rate as an index of light anesthesia or hypovolemia are unreliable. Indirect drug effects that depend on autonomic pathways are absent eg. the chronotropic effects of atropine, pancuronium or opioids.

Cardiac output is dependent on venous return and circulating catecholamines so it is important to carefully administer or avoid beta blockers.[16] For treatment of hypertension other drugs are usually

recommended. Cardiac drugs exert direct effects only. These drugs include epinephrine, isoproterenol, norepinephrine, and dopamine. Ephedrine (which has both indirect and direct effects) exerts it's direct effects only. Compensation for changes in blood volume and cardiac filling pressure is limited and delayed. Hypovolemia is poorly tolerated in these patients. Table 3 shows response to commonly used drugs on the denervated heart.

Agent	**Sinus rate**	**AV conduction**	**Hemodynamic Effect**	**Comment**
Atropine	-	-	-	+ Muscarinic effects
Calcium Channel Blockers	↓	↓	↓ SVR may not change BP	
Digoxin	-	Initial – Chronic ↓		
Dobutamine	↑	↑	↑ CO ↑ BP	HR effect greater than in normal heart; useful in detecting coronary insufficiency
Dopamine	↑	↑	↑ CO may ↑ BP	Often useful during separation from CPB and early ICU
Epinephrine	↑	↑	↑ BP and CO	
Isoproterenol	↑	↑	↓ BP may ↑ CO	
Norepinephrine	↑	↑	↑ BP may ↑ CO	
Nitroprusside	-	-	↓ BP may ↑ CO	
Phenylephrine	-	-	↑ BP variable effect on CO	
Procainamide	↓	↓		
Propranolol	↓	↓	Usually ↓ CO ↓BP	

Table 3 Cardiovascular effects of various pharmacologic agents on the denervated heart. AV = Atrioventricular; SVR = Systemic vascular resistance; BP = blood pressure; CO = cardiac output; CPB = cardiopulmonary bypass.[33]

Coronary Vasculopathy

Coronary vasculopathy remains the leading factor affecting the long-term survival of heart transplant recipients.[34,35,36,37] It is associated with congestive heart failure, silent myocardial infarction and sudden death.[7,35] Although the etiology of coronary vasculopathy is multifactorial, recurrent graft rejection is a major contributing factor. Early multiple rejection episodes between 3 and 12 months post transplant strongly correlated with the development of severe coronary vasculopathy.[38] In the same pediatric population, late severe rejection (> 1 year post transplant) or late multiple rejections are risk factors for coronary vasculopathy.[7] Furthermore these patients develop coronary vasculopathy soon after the rejection episode. Their risk of sudden death warrants immediate re-listing for retransplantation once coronary vasculopathy is diagnosed.[7] The incidence of coronary vasculopathy in pediatric transplant

recipients varies widely and usually parallels the follow up duration.[7] In the Loma Linda pediatric transplant population, the freedom from coronary vasculopathy is 92% and 75% at five and ten years respectively. Coronary vasculopathy accounts for one third of all deaths occurring more than one year post transplant.[7,34] Transplanted infants were shown to be at lower risk for coronary vasculopathy but at greatest risk of death after the diagnosis of coronary vasculopathy is made.[34]

The gold standard for evaluating coronary artery disease has been angiography. However, this modality may underestimate the degree of diffuse intimal hyperplasia in transplanted patients with coronary vasculopathy.[39] Coronary intravascular ultrasound (IVUS) has been establised as a very useful and reliable modality for evaluating coronary vasculopathy. Although it is often combined with angiography, IVUS is more sensitive in detecting early intimal disease.[40,41,42] Dobutamine stress echocardiography (DSE) has been shown to be a safe and reliable screening method for coronary vasculopathy in children.[39,43,44] A negative DSE predicts short-term freedom from cardiac events in pediatric transplant patients.[43] Of interest, it has been noted that pediatric transplant patients have baseline regional wall motion abnormalities at rest in the absence of coronary vasculopathy, that resolve during DSE.[39] This may imply subclinical coronary insufficiency in these patients.

Patients who present for an urgent or semi-elective operation with a positive DSE, IVUS, or angiographic evidence of coronary vasculopathy are a special challenge. These children may be on antirejection and other medical therapies that should be continued perioperatively. The anesthesia management should parallel the approach used for adults with coronary artery disease. Detection of intraoperative myocardial ischemia may be problematic. Monitoring the electrocardiogram for ST changes consistent with ischemia is of some value. Unexplained hypotension should raise suspicion of myocardial ischemia. Treatment of suspected intraoperative myocardial ischemia is directed at improving the balance of myocardial oxygen supply and demand. TEE is a more sensitive monitor for changes in cardiac function than hemodynamic changes in children undergoing cardiac surgery[45], and may be of benefit for high risk patients with previous cardiac transplant undergoing other surgical procedures. The use of calcium channel blockers (diltiazem) and nitroglycerin may be indicated.

Graft Rejection

Rejection is responsible for approximately 30% of deaths following cardiac transplantation in children. Although the majority of rejection episodes occur within the first 3 months of transplantation, the peak time is approximately 4 to 6 weeks posttransplantation. Usually these episodes will involve increasing immunosuppressive therapy, possibly adding additional drugs, such as methotrexate and augmentation of steroid use.[46]

There is variability in the sensitivity and specificity of echocardiography in detecting rejection in pediatric patients. No single echocardiographic index has been shown to be predictive of significant rejection. However, use of a multiparametric, two-dimensionally guided, m-mode analysis algorithm based on changes from baseline has been shown to be highly predictive of cellular changes of rejection.[47] Endomyocardial biopsy may be indicated when diagnosis of rejection cannot be made non-invasively.

It has been questioned whether endomyocardial biopsies are needed annually. A recent survey of 1,108 biopsies performed in 269 children showed that 8 to 10% of the patient population had positive biopsies up to 10 years of follow-up despite being asymptomatic.[48] These biopsies showed evidence of moderate rejection. The question is whether moderate rejection requires treatment in a clinically healthy patient. The current protocol at Loma Linda is to treat all biopsy proven moderate rejection to prevent progression to a more severe rejection episode. Patients who have had severe acute rejection episodes are at higher risk for development of coronary vasculopathy.[49] Late severe rejection is an independent predictor of coronary vasculopathy.[43] If this subclinical rejection is not treated it may be an important contributor to the development and progression of post transplant coronary vasculopathy. Therefore annual monitoring with endomyocardial biopsy is still recommended.

Arrhythmias are more prominent during episodes of rejection, and this can compound the intraoperative morbidity in patients undergoing noncardiac surgery. Graft failure associated with rejection is another risk factor for patients undergoing noncardiac surgery. This is particularly true when anesthetic agents are used that may contribute to myocardial depression. Patients must be scrupulously evaluated for the presence of graft failure and treated appropriately before general anesthesia is considered. Adequate levels of imunosuppressive agents should be maintained throughout the perioperative period.

Cardiac Dysrhythmias

Cardiac dysrhythmias in adult heart transplant recipients are common and have been used as a predictor of rejection. Less is known in the pediatric population, however approximately 40% of pediatric patients have been found to have arrhythmias including supraventricular and ventricular tachyarrhythmias, sinus brady arrrhythmias, and Wenckebach 2nd degree AV block.[50,51] Results suggest that the onset of arrhythmias should prompt a search for coronary vasculopathy or rejection.[50,51] Pediatric transplant patients must be monitored closely for the development of dysrhythmias and treated aggressively.[37]

A small subset of pediatric transplant recipients (3%) require permanent pacemakers.[38] The type of pacemaker present and the likely response to electrocautery must be determined before induction of anesthesia. If necessary, the pacemaker should be reprogrammed to the VVO mode before use of electrocautery. If patients do develop bradyarrhythmias, direct beta-adrenergic-stimulating agents, such as epinephrine or isoproterenol, may be used. Antiarrhythmics and cardioversion may be used to successfully treat dysrhythmias. If rejection is the underlying cause it must be treated.

Malignancy

Malignancy accounts for mortality in 1-4% of pediatric heart transplant patients. However, the recent data lists cause of death at >5 years post transplant to be 9% of deaths from lymphoma and 3.8% for other malignancies.[34] Overall the majority of tumors were lymphomas with the rest carcinomas.[52] Of the lymphomas tested, all manifested signs of Epstein-Barr virus infection. The incidence of malignancy at Loma Linda is 6.5% with all but one case being lymphoproliferative disease. Ten year actuarial freedom from post-transplant lymphoproliferative disease is 91.6% at Loma Linda. Treatment of malignancies includes reducing immunosuppression alone but a percentage of patients received radiation therapy. Acyclovir or ganciclovir was administered to 100% of patients with lymphoma. Of the patients with malignancies 45% died. More recently with aggressive decrease in immunosuppressive agents (6-8 weeks), treatment with anti CD20 monoclonal antibody and low dose chemotherapy as indicated, the survival rate is 80% in the Loma Linda statistics. After treatment for the malignancy has been completed many of these patients are started on sirolimus (Rapamune®) alone for immunosuppression. However, between 20-50% of malignancies are discovered incidentally at autopsy suggesting there is a higher incidence of subclinical disease.[18,53]

Preoperative Management

Pediatric transplant recipients presenting for a noncardiac procedure may have a very complicated medical history requiring an integration of several critical considerations. On the other hand, prior heart transplant may be their only medical history. The need for preanesthetic medication becomes a matter of clinical judgment taking into consideration the child's emotional needs, hemodynamic stability, and the anticipated action of the medications given. Some children may have received sufficient steroid therapy recently to have suppressed the hypothalamic - pituitary axis, therefore requiring stress steroid replacement by any of the accepted protocols.

All children should receive basic cardiovascular and respiratory monitoring. The benefits of invasive monitoring should be weighed against the added risk of infection with its potentially serious complications in this population. These children will be followed closely by pediatric cardiologists. They may be followed by or in conjunction with transplant centers whose protocols for detection of

rejection and coronary vasculopathy will vary by institution. Having access to the patient's current medical record can be helpful but is never a guarantee of an uneventful anesthetic course.

Intraoperative Management

The intraoperative anesthetic strategy for these children is dictated by their underlying surgical diagnosis and any other complicating factors that may be present. Modifications may be necessary to address concomitant conditions such as reflux, full stomach, increased intracranial pressure, or the diagnosis of coronary vasculopathy, graft failure or rejection. Medications and monitoring choices will need to be tailored in these children to limit anesthetic morbidity. In our experience[54], medically stable patients undergoing noncardiac, nonthoracic surgery after cardiac transplantation undergo the same surgical procedures as similarly aged nontransplantation patients. Moreover, similar induction techniques, including sodium thiopental, inhalational agents, and routine monitoring techniques, may be used in a large number of these patients with no apparent direct anesthetic-related complications.[54]

Reversal of muscle relaxation can be performed safely without the use of muscarinic antagonists.[31,54] Bradycardia after neostigmine use has been reported in an adult heart transplant recipient.[55] However as parasympathetic reinnervation has not been shown to occur in humans. Routine use of muscarinic antagonists would mostly be beneficial to block the muscarinic side effects of anticholinesterases.

Caution should be used with anesthetic agents with significant negative inotropy as these may limit the heart's ability to respond to changes in end diastolic volume. Reflex mechanisms to compensate for the inherent depressant effects of some anesthetic agents are not functional due to cardiac denervation. Preservation of intravascular volume is essential as cardiac output relies on venous return. Signs of light anesthesia or hypovolemia, such as tachycardia, will be delayed until circulating catecholamines can influence the cardiac beta-receptors directly and will persist longer after appropriate treatment.[56] Sevoflurane for induction with desflurane or isoflurane for maintenance is a safe combination.

The same potential hazards apply to regional techniques employed in heart transplant recipients. The rapid changes in preload and systemic vascular resistance that accompany spinal or epidural anesthesia represent a significant threat of hypotension with a heart devoid of sympathetic reflex compensation.[57] Conversely, rapid fluid administration may precipitate diastolic dysfunction in transplanted hearts manifesting occult restrictive hemodynamics.[58] Given sufficient augmentation of circulating volume, a block with more gradual, controllable onset (eg., epidural versus spinal), and prompt recognition and treatment of hemodynamic disturbances with direct-acting sympathomimetic agents, would seemingly provide the greatest safety. Nevertheless, both spinal and epidural techniques have been safely employed. As with any intervention in these children, attention to their vulnerability to microorganism invasion dictates isolation precautions.

In the absence of other complicated medical issues, same-day surgery is safe in pediatric heart transplant recipients.[54] However, in patients with chronic rejection, significant coronary artery disease, or a history of graft failure, overnight monitoring in a hospital setting will be needed even if only a minor surgical procedure was performed.[54]

In conclusion, for patients with transplanted hearts it is important to maintain normovolemia and to avoid high doses of drugs that have direct cardiac depressant effects such as halothane and lidocaine. It is also important to maintain afterload and avoid agents that cause rapid changes in vascular tone. Direct acting agents should be used as cardiotonics if needed making isoproterenol and dopamine good choices. If the patient has a pacemaker it must be reprogrammed to the VVO mode before using surgical cautery. An acceptable anesthetic technique is a narcotic/relaxant technique although low dose inhalational agents can be added realizing that higher doses of inhalational agents may cause severe myocardial depression. It is very important to monitor neuromuscular blockade especially in patients that are on immunosuppressive drugs that may effect the duration and the action of muscle relaxants.

Special Considerations for the Patient with a Transplanted Liver

Patients that have had successful liver transplants have normal metabolic and drug metabolism and any anesthetic regimen can be used. It is very important to maintain careful aseptic technique because these patients are prone to developing cytomegalovirus, Epstein-Barr virus, or hepatitis virus infections. If surgery is needed in the first few weeks after liver transplantation in small children and infants blood pressure should be kept in the normal range and hemoconcentration avoided to decrease the risk of hepatic artery thrombosis.

However, if the patient does have abnormal liver function this will result in abnormal drug distribution, protein binding, metabolism and decreased clearance of many of our anesthetic agents. Another problem in the patient with abnormal liver function is coagulopathy. A good screening test is the prothrombin time (PT) which is prolonged before other tests are abnormal and allows us to quantitate the amount of liver dysfunction. Acute rejection is also manifest by cholestatic jaundice, increased liver enzymes, eosinophilia and lymphocytosis. Caveats to anesthetic management are cautious use of volatile agents, and the realization that the response to opioids can be unpredictable. Cisatracurium is the muscle relaxant of choice in patients who have abnormal liver function.

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