This Heart Transplant Is Ruining My Appendectomy

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Objectives:

1. Describe anesthetic concerns of children after heart transplant
2. Discuss anesthetic implications of immunosuppressant medications
3. Discuss concerns of organ rejection and the anesthetic implications
4. Discuss the risk of coronary artery disease after heart transplant

Case History:

6 year old female, underwent heart transplant two years ago for dilated cardiomyopathy, presents for appendectomy. She is vomiting and has a WBC count of 24. Oxygen saturation is 92% on room air. No prior anesthetic records are available.

Questions:

What further information would you like for your preoperative evaluation? What are the hemodynamic goals post-transplant? Does this patient need a rapid sequence induction? Are you concerned about bradycardia with succinylcholine? If it occurs, how should it be treated? How long does the denervation post transplant last?

Case History (continued)

This 6 year old female, 19 kg, was last hospitalized two months ago for acute rejection. She has improved and remains on increased prednisone dose, tacrolimus, and mycophenolate mofetil.

The parents are Korean speaking only and an interpreter is present. There is no family history of anesthetic problems. On physical exam, she is sitting up in the stretcher vomiting. No syndromic features noted. Chest shows a sternotomy scar, no wheezes/rales/rhonchi appreciated on exam. + hepatomegaly. There is no murmur present and her capillary refill is > 2 seconds. Temperature is 38.5, HR 110, BP 095/56, SpO2 92% on room air.

Echocardiogram (prior to discharge from episode of acute rejection): s/p Heart transplantation. Mild left atrial enlargement.
Mild to moderate TR. Peak tricuspid valve insufficiency gradient is 30 mmHg. Normal right ventricle structure and size. Mild concentric left ventricular hypertrophy. Normal right and left ventricular systolic function. Borderline diastolic function

Questions:

How is acute rejection diagnosed? How is it treated? Is there a role for IVIG? Does this patient need stress dose steroids? What is the mechanism of action of tacrolimus and mycophenolate mofetil? Do these medications have an impact on the anesthetic

management of this patient? Does this patient need pre-op labs, CBC, LFT's? Are you concerned about pulmonary hypertension based on this echo? Is the hepatomegaly of concern? Could this represent heart failure due to another episode of rejection? Is laparoscopic technique of significance in this case? Do you want an EKG prior to the procedure? What are you concerned about on the EKG?

Intraoperative Care:

After standard monitors are placed and she is pre-oxygenated, she undergoes a rapid sequence induction with etomidate and succinylcholine and is intubated without difficulty. The procedure commences without event.

Questions:

Does this patient need an arterial line? Intraop five lead EKG? Can a three lead EKG be adapted to a five lead EKG?

Intraoperative Care (continued):

The patient soon becomes hypotensive (55/37). A 20 cc/kg crystalloid bolus is given with minimal improvement. The HR is 130. The Sevoflurane inhalational anesthetic is at 1.8

Questions:

What is the differential diagnosis of the hypotension? Can it be attributed to the inhalational agent? Could this be a result of her medications? What is the appropriate management at this point? Additional IVF? Phenylephrine? Epinephrine? Isoproterenol?

Intraoperative Care- Postoperative Care

The blood pressure normalizes and the case finishes uneventfully. She is extubated and transferred to the recovery room on face mask oxygen.

Questions:

Should nondepolarizing muscle relaxants be reversed? Are you concerned about the potential bradycardia from the neostigmine? Is the PACU an appropriate place for recovery for this patient or does she need ICU? What are your concerns postoperatively for this patient? If she began to complain of chest pain what should the initial steps be in management?

Discussion:

The most common indications for pediatric heart transplant include congenital heart disease, such as hypoplastic left heart syndrome, and cardiomyopathy. Children undergoing transplant for cardiomyopathy tend to be older children compared to the congenital heart disease transplant patients. According to the 2010 UNOS data approximately 300 children receive heart transplants each year.

As the number of children who have undergone a solid organ transplant increases the frequency with which these children will require surgery unrelated to the transplanted organ increases. The perioperative management of these patients includes awareness of the potential complications related to immunosuppressive medications, potential for rejection and risk of infection.

Immunosuppression is a component of all post transplant medication regimens however; the particular medication regimen can vary. The most common medications used for immunosuppression include: steroids, antiproliferative agents, calcineurin inhibitors, TOR inhibitors, IL-2 receptor antagonists and monoclonal antibodies.

Corticosteroids

Steroid therapy is a standard component of induction, maintenance, and antirejection therapy in heart transplant recipients. High-dose steroids are generally administered intraoperatively and postoperatively with gradual tapering of doses. Additionally, steroids are usually the first treatment for moderate rejection (grade 3A or 3B) without hemodynamic compromise. Approximately 80% to 85% of these rejection episodes respond to the initial corticosteroid regimen (1,2)

Side effects steroids: Hypertension, emotional lability, cataracts, gastric ulcer, poor wound healing, and proximal myopathy

Cosmetic effects include hirsutism, acne, easy bruising, skin fragility, moon face, buffalo hump, weight gain, and truncal obesity.

Metabolic effects include hyperlipidemia, salt and water retention, diabetes mellitus, osteopenia, and growth retardation in children (3,4) Long-term administration of steroids may result in chronic adrenal suppression.

Antiproliferative Agents

Antiproliferative agents are those that directly or indirectly inhibit the expansion of alloactivated T-cell and B-cell clones.

Azathioprine and mycophenolate mofetil have similar mechanism of action in that each acts by interfering with purine synthesis.

Side effects of AZA: myelosuppression, including leukopenia, anemia, and thrombocytopenia. Pancreatitis, hepatitis, and hepatic veno-occlusive disease are rare.

Mycophenolate mofetil is a selective inhibitor of the de novo pathway of purine biosynthesis and is therefore more specific and is a potent inhibitor of T-cell and B-cell proliferation

Side effects mycophenolate mofetil: nausea, vomiting, and diarrhea, which usually are responsive to a decrease in dosage (5) The toxicity of MMF may be more closely related

to the mycophenolic acid levels than the dose. The risk of opportunistic infections appears to be higher in patients treated with MMF when compared with AZA.

Calcineurin Inhibitors (Cyclosprorine and Tacrolimus)

These complexes bind to calcineurine, an enzyme in T-cell IL-2 production (6) resulting in the inhibition of cytokine transcription by the CD4 cell. The blockade of cytokine production and cytokine receptor expression inhibits T-cell proliferation and differentiation so that the immune responses are not activated.

Side effects of CSA:

Acute nephrotoxicity occurs secondary to intrarenal vasoconstriction and is reversible. Chronic nephrotoxicity is likely a long term secondary consequence of persistent renal vasoconstriction and ischemia and is irreversible with obliterative vasculopathy and interstitial fibrosis on histology (25).

Cardiovascular adverse effects include hypertension and effects on coagulation with an increase in the incidence of deep venous thrombosis (7). Cyclosporine induced hypertension is thought to be caused by renal vasospasm (8) Nearly 75% of cardiac post-transplant recipients develop mild to moderate hypertension as a result of cyclosporine therapy (9)

Neurologic complications include tremor, headache, convulsions, and various paresthesias of the limbs.

Hyperkalemia is associated with cyclosporine (10) and is reversible by lowering the dosage. Hyperglycemia may occur and is also reversible. Elevated serum urate levels may occur as a result of tubular defect associated with cyclosporine nephrotoxicity and may result in gout.

Hepatic toxicity consists of asymptomatic mild reversible elevations in bilirubin and occasionally transaminases suggesting cholestasis (11) Central nervous system neurotoxicity can manifest as headache, paresthesias, tremor, confusion, flushing and seizures and may be present in half of the patients (12,13,14,15)

Tacrolimus (FK506) inhibits T cell lymphocyte proliferation but is 100 times more potent than CSA (16). It is used as first line immunosuppression in cardiac re-transplant patients and those patients who have side effects from CSA therapy. There should be a 12-48 hour window from stopping CSA to starting tacrolimus.

Side effects of Tacrolimus: nephrotoxicity is equivalent to CSA. Tacrolimus induces a higher incidence of diabetes mellitus and neurotoxicity but a lower incidence of hypertension, hyperlipidemia, hirsutism, and gingival hyperplasia (17) Alopecia, bone marrow suppression, increased lymphoproliferative disease and infectious diseases are other associated side effects.

TOR Inhibitors

TAC was previously known as FK506. It is a macrolide and is produced by the fungus *Streptomyces tsukubaensis.* (see above for details)

Sirolimus 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

IL-2 Receptor Antagonists

Basiliximab and Daclizumab can be used for induction therapy post transplant and are given close to the time of the initial transplant.

Monoclonal Antibodies

OKT3 a monoclonal antibody directed against the a chain of CD3 molecule, which functions to modulate the receptor and inactivate T-cell function. OKT3 blocks not only the function of naive T cells but also the function of established cytotoxic T cells (24).

Side effects OKT3: Cytokine release syndrome is perhaps the most well known complication of OKT3 and is the result of a release of T-cell cytokines. Cytokine release syndrome is characterized by fever, chills, general weakness and mild hypotension. Less common side effects include: vomiting, diarrhea, and rarely bronchospasm or severe hypotension. As with any immunosuppressant regimen, the likelihood of an opportunistic infections is elevated.

Anesthetic Implications
Immunosuppressant's can impact the pharmacology of multiple anesthetic agents and it is therefore important to have an awareness of these effects.

Drugs that Affect Cyclosporine and Tacrolimus Blood Levels

Increase Blood Levels	**Decrease Blood Levels**
Bromocryptine	Carbamazepine
Chloroquine	Octreotide (may not interact with Tacrolimus)
Cimetidine (may not interact with CSA)	Phenobarbital
Clarithromycine	Phenytoin
Co-trimoxazole	Rifampycin
Danazole	Ticlopidine (may not interact with tacrolimus)
Diltiazem	
Erythromycin	
Fluconazole	
Itraconazole	
Ketoconazole	
Metoclopramide	
Nicardipine	
Verapamil	

Table from: (19) Kostopanagiotou et al. Anesthesia in Nontransplant Surgery and Transplanted Patients. Anesth Analg 1999; 89: 614

Side Effects of Immunosuppresives That Have a Direct Impact on Anesthetic and Perioperative Management

	CyA	Tacr	Aza	Ster	MMF	ATG	OKT3
Anemia	-	-	+	-	+	-	-
Leucopenia	-	-	+	-	+	+	+
Thrombocytopenia	-	-	+	-	+	-	-
HTN	++	+	-	+	-	-	-
Diabetes	+	++	-	++	-	-	-
Neurotoxicity	+	+	-	+	-	-	-
Renal Insufficiency	+	++	-	-	-	-	-
Anaphylaxis	-	-	-	-	-	+	+
Fever	-	-	-	-	-	+	+

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Cyclosporine has been noted to potentiate the effect of barbituates and fentanyl in mice but the mechanism is unclear. It is known that cyclosporine enhances muscle relaxants. (19)

The following drugs may cause renal dysfunction when administered with tacrolimus or cyclosporine: Amphotericin, Cimetidine, Ranitidine, Melphanan, NSAIDS, Co-trimoxazole, Vancomycin, Tobramycin, Gentamycin, tacrolimus or cyclosporine. (19)

The Perioperative management of these patients includes not only an awareness of the anesthetic implications of immunosuppressive medications but also a comprehensive assessment of graft function, rejection, presence of infection, and multi-organ function.

If the function of the transplanted organ is abnormal, rejection should be suspected. Organ rejection results in a progressive decline and is the main cause of late mortality for transplant recipient patients. Rejection is categorized into hyperacute, acute and chronic types.

Chronic rejection usually presents as accelerated coronary artery disease (CAD) and therefore transplant recipients may have myocardial ischemia without any clinical symptoms. Mild rejection does not compromise contractility but severe rejection can lead to both systolic and diastolic dysfunction. Clinically rejection can present with fatigue, ventricular dysrhythmias, heart failure, myocardial infarction or death. Annual endomyocardial biopsies are recommended.

These patients also, as previously mentioned, can have accelerated CAD and coronary vasculopathy remains the leading factor affecting the long-term survival of heart transplant recipients (20, 21). Early multiple rejection episodes between 3 and 12 months post transplant correlate with the development of severe CAD (22). According to Mulla et al, in the pediatric population, late severe rejection (> 1 year post transplant) or late multiple rejections are risk factors for CAD (23). Transplanted infants are at lower risk for CAD but at highest risk of death once diagnosed with CAD (20). The gold standard for evaluating CAD is angiography. Patients with CAD who present for emergent surgery should be closely monitored intraoperatively and if an episode of unexplained

hypotension occurs the anesthesiologist should be concerned regarding the possibility of ischemia.

Specifically with regard to heart transplantation the transplanted heart has no sympathetic, parasympathetic, or sensory enervation and the loss of vagal tone results in a higher than normal resting heart rate. The intrinsic mechanisms and coronary autoregulation remains intact post transplant. Carotid massage and valsava have no effect on the heart rate. Additionally, there is loss of cardiac baroreflexes and loss of sympathetic response to laryngoscopy. The heart rate response to inadequate anesthetic depth or analgesia may be blunted.

Epinephrine, Isoproterenol and dobumatime are effective in both normal and denervated hearts. Ephedrine has a blunted response on blood pressure and heart rate in transplant recipient patients. Atropine is ineffective. Although, bradycardia from neostigmine has been reported, it has also been noted not to occur in these patients.

Volatile anesthetics are known myocardial depressants but are usually well tolerated in these patients. However, it is important to be aware that the heart may have limited ability to compensate. Preservation of intravasulcar volume is important as the cardiac output relies upon venous return and circulating catecholamines, therefore caution should be exercised with regional anesthesia as well.

In conclusion, pediatric patients who have undergone heart transplantation can be safely anesthetized for surgical procedures however, it is important to be aware of the hemodynamic complications, immunosuppressant medication interactions, concern for rejection or CAD, and potential for infection in these patients.

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