Heart Transplant in Children: What a Primary Care Provider Needs to Know

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ABSTRACT

Heart transplantation is offered to children with heart failure that is not amenable to medical or surgical therapy. Indications for heart transplant include unrepairable congenital heart disease, failed palliation of congenital heart disease, and cardiomyopathies. There has been tremendous progress in this field since the first heart transplant was performed in 1967. Each year, approximately 500 pediatric heart transplants take place worldwide. Pediatric heart transplant survivors are living longer with their initial transplant. Many pediatric practitioners are faced with caring for these patients before as well as after the heart transplant and, therefore, they should be knowledgeable about basic principles related to heart transplant. There are certain complications that are unique to this population, and medication side-effects, evaluation and management of a febrile illness, opportunistic infections, vaccination, pregnancy, and exercise recommendations are areas that require special consideration. [Pediatr Ann. 2018;47(4):e172-e178.]

The first pediatric heart transplant was performed in 1967.¹ Since then, more than 12,000 pediatric heart transplants have been reported to the registry of the International Society for Heart and Lung Transplantation;¹ and since the early 1990s there have been approximately 500 pediatric heart transplants performed annually worldwide.¹ Heart transplant is offered to children who develop heart failure secondary to cardiomyopathy that cannot be controlled with medical therapy alone, children with congenital heart disease that may not be amenable to surgical repair, and for failed palliation of congenital heart disease. Based on data from 1990 to the present, overall median survival ranges from 12 to 21 years for pediatric heart transplant recipients, with better survival seen in infants.¹

It is likely that pediatricians will need to provide care for some of these children with heart disease before or after heart transplant. This article is a brief review on heart transplant for the benefit of pediatricians.

HISTORICAL PERSPECTIVE

Dr. Adrian Kantrowitz performed the first pediatric heart transplant in a neonate with tricuspid atresia in the United States in 1967, 3 days after Dr. Christian Bernard performed the first human-to-human adult heart transplant in South Africa.² In 1984, Dr. Leonard Bailey performed a xenotransplant with a baboon heart into a neonate who survived for 20 days. In the same year, Dr. Denton Cooley performed the first successful infant heart transplant, and that child survived for 13 years.²

In the US, The National Organ Transplant Act was passed by Congress in 1984.³ This act prohibited the selling of human organs, established the Organ Procurement and Transplantation Network to ensure fair and equitable allocation of donated organs, and established the Scientific Registry of Transplant Recipients to conduct an ongoing evaluation of the scientific and clinical status of organ transplantation.

IMMUNIZATION

Vaccine-preventable diseases can be a major source of morbidity and mortality in transplant recipients.⁴ Immunosuppression regimens used after heart transplant impair both the T and B cell
It is recommended that health care providers, siblings, and other family members (including pets) of patients with heart transplant should receive all age-appropriate vaccines, and a nonlive vaccine option is preferable. For example, injectable influenza vaccine should be administered in place of nasal influenza vaccine. Annual influenza vaccine is highly recommended for all close contacts. If for any reason inactivated vaccine cannot be administered, the live attenuated nasal influenza vaccine may be administered, and people who are vaccinated should take all the precautions to prevent the spread of vaccine virus, such as frequent handwashing, for 2 weeks after vaccination. Similarly, rotavirus antigen is present in stool after oral rotavirus vaccine, so proper hand washing after diaper changes for 2 weeks after vaccination is recommended to prevent transmission to the child with a heart transplant. As for MMR and varicella vaccines, which are only available as live virus vaccines, it is important that close contacts receive these vaccines to prevent the patient with heart transplant from being infected with wild-type viruses. If the vaccinated patients develop rashes after these vaccines, appropriate infection control precautions are recommended.

Children younger than age 2 years who undergo cardiac transplantation during the respiratory syncytial virus (RSV) season may be considered for palivizumab prophylaxis. Travel vaccines such as yellow fever, oral Salmonella typhi, and oral cholera vaccines are live vaccines and are not recommended after transplant. However, injectable Salmonella typhi, Japanese encephalitis, and injectable cholera vaccines are inactivated vaccines and can be administered prior to travel to endemic areas. For more details on individual vaccines, the reader is referred to the article by Danziger-Isakov and Kumar.

INFECTIVE ENDOCARDITIS PROPHYLAXIS

There are limited data regarding the incidence of infective endocarditis (IE) in children after heart transplant. The data from pooled case reports in adult heart transplant recipients show a higher incidence of IE as compared to the general population. As per the American Heart Association guidelines published in 2007, it is recommended that all children undergoing heart transplant who develop valvulopathy should receive IE prophylaxis for all dental procedures that involve manipulation of gingival tissue, the periapical region of teeth, or perforation of the oral mucosa. Antibiotic prophylaxis is reasonable to use for procedures on the respiratory tract or on infected skin, skin structures, or musculoskeletal tissue. Antibiotic prophylaxis used solely to prevent IE is not recommended for genitourinary or gastrointestinal tract procedures. A discussion with the specific transplant center may be helpful for understanding the policy on prophylaxis.

COMPLICATIONS OF HEART TRANSPLANT

Complications of heart transplant can be divided into acute and long term. Acute complications could be caused by the adverse effects of medications or those associated with immunosuppression. Almost all of the immunosuppressant medications cause hypertension. Diabetes mellitus and renal dysfunction are seen with calcineurin inhibitors such as cyclosporine and tacrolimus; dyslipidemia is associated with calcineurin inhibitors and sirolimus; hypomagnesaemia requiring supplementation is seen with calcineurin inhibitors; and bone disease induced by steroids is not uncommon. Hypertension and dyslipidemia are primarily managed by the transplant cardiologist, whereas diabetes

responses of the immune system. Therefore, both the efficacy and safety of vaccines need to be taken into consideration prior to their administration.

Depending on the the child’s age at the time of the heart transplant, they may be partially immunized or not immunized at all. For all children awaiting heart transplant, including neonates, an accelerated vaccination schedule should be prepared in consultation with infectious disease specialists, and the vaccines administered while awaiting heart transplant. Children awaiting heart transplant who are not hospitalized are frequently referred to their primary care provider for immunization.

Vaccination may be resumed 3 to 6 months after transplant, by which time maintenance immunosuppression should be established. These children should never receive live vaccines (ie, measles-mumps-rubella [MMR], varicella, live influenza, and oral rotavirus) after transplantation because they remain on lifelong immunosuppressive therapy; however, they should receive all age-appropriate nonlive vaccines and yearly inactivatable influenza vaccine. Partially immunized or nonimmunized patients can develop life-threatening infections from vaccine-preventable infections such as varicella. This should be kept in mind when evaluating patients for rashes or unusual symptoms and signs. Likewise, if a sick contact with a vaccine-preventable disease is identified, the child should be evaluated for possible infection.

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and bone disease require active engagement of an endocrinologist and orthopedic surgeon, respectively.

Complications associated with immunosuppression can arise as a result of too much or too little immunosuppression. Overly immunosuppressed patients develop recurrent and serious infections and certain malignancies, the most common being posttransplant lymphoproliferative disease (PTLD), whereas patients who are not optimally immunosuppressed develop graft rejection and potentially coronary allograft vasculopathy (CAV).

Acute allograft rejection is common in the first year after transplant, with 15% to 20% of the patients requiring treatment. This incidence decreases significantly after the first year. Allograft rejection can be cellular or antibody-mediated (previously known as humoral rejection), with the latter being more commonly associated with hemodynamic compromise and accelerated CAV.\textsuperscript{15,17} Rejection can be asymptomatic and detected only on surveillance endomyocardial biopsies, but when symptomatic it presents with symptoms of low cardiac output (ie, poor feeding, vomiting, abdominal pain, fatigue). Physical examination findings in these patients include tachycardia, S3 gallop, a new murmur from mitral or tricuspid valve regurgitation, hepatomegaly, and in severe cases signs of pulmonary edema. The transplant center should be notified if there is suspicion for rejection as prompt treatment can improve the outcomes. Patients with suspected rejection undergo cardiac catheterization and endomyocardial biopsies for grading of rejection, if present. Rejection is typically treated with high-dose intravenous methylprednisolone and use of antithymocyte globulin in severe cases. Intravenous immunoglobulin and plasmapheresis are reserved for antibody-mediated rejection.

CAV is a chronic graft complication that leads to progressive diffuse narrowing of the coronary arteries. It is believed to be a result of chronic immune rejection and nonimmune factors like hypertension, dyslipidemia, and diabetes.\textsuperscript{18} CAV is the leading cause of graft failure in heart transplant recipients and can be definitively treated by retransplantation only, although certain therapies such as the use of statins and incorporating sirolimus into the immunosuppression regimen have been shown to be beneficial in halting or slowing the progression of CAV.\textsuperscript{19} Patients with more discrete stenosis undergo revascularization of the coronary arteries by angioplasty and stent placement as a palliative solution and bridge to retransplantation.\textsuperscript{20,23}

PTLD encompasses a spectrum of malignancies in children after solid organ transplantation. The most common form is associated with unchecked proliferation of Epstein-Barr virus (EBV)-infected B cells due to absence of EBV-specific T-cell cytotoxic effects due to immunosuppression.\textsuperscript{24} PTLD management requires a multidisciplinary approach, with the oncologist in the leading role. Patients may be asymptomatic with EBV viremia or present with recurrent fevers, weight loss, fatigue, and lymphadenopathy. PTLD can also present as adenotonsillar enlargement.\textsuperscript{25}

**TRANSPLANT MEDICATIONS AND COMMON ADVERSE EFFECTS**

Lifelong immunosuppression is required after heart transplantation. Typical medication combinations for posttransplant immunosuppression include calcineurin inhibitors (tacrolimus, cyclosporine) as a primary agent, and mycophenolate mofetil, azathioprine, or sirolimus as a secondary agent. Azathioprine is only occasionally used as a secondary immunosuppressant agent, as mycophenolate and sirolimus have proven to be superior at reducing the onset and progression of coronary artery vasculopathy.\textsuperscript{26} Patients also take corticosteroids for a variable duration immediately after transplantation. Calcineurin inhibitors are dosed based on serum trough levels, so strict adherence from patients and families is required in regard to taking medications at scheduled time. Reinforcement from the pediatrician regarding medication compliance is helpful in this regard.

Immunosuppression is most intense during the first year after cardiac transplant. Patients require bacterial, viral, and fungal prophylaxis to prevent infections with opportunistic organisms. Mucocutaneous candidiasis (thrush), and infections with cytomegalovirus (CMV) and other herpesviruses, *Pneumocystis jiroveci*, and *Toxoplasma gondii* are of particular concern. Prophylaxis typically includes nystatin, valganciclovir, and trimethoprim/sulfamethoxazole. CMV prophylaxis duration ranges from 3 to 6 months depending on the patient’s and donor’s serologies at the time of transplantation. Trimethoprim/sulfamethoxazole use is variable among pediatric and adult heart transplant centers, with duration ranging from 3 months to many years. Nystatin is commonly prescribed for the duration of medium to high-dose steroids. In the setting of a sulfa allergy or glucose-6-phosphate dehydrogenase deficiency, alternative regimens including aerosolized pentamidine isethionate, dapsone (diaminodiphenylsulfone) with or without trimethoprim, or pyrimethamine can be used.\textsuperscript{26}

Immune-suppressive agents have a narrow therapeutic window. Supratherapeutic doses can cause severe side effects, whereas subtherapeutic doses pose a risk of rejection.\textsuperscript{14} Tacrolimus frequently causes hypertension, electrolyte disturbances (hyperglycemia, hyperkalemia, hypomagnesaemia), de-
layed wound healing, and serious infections. Tremors and arthralgia are seen in some patients taking tacrolimus. Renal dysfunction is of great concern as supra-therapeutic levels are highly nephrotoxic. Keeping a patient well hydrated is important, especially if there is inter-current acute gastroenteritis.

Mycophenolate mofetil has a fairly high incidence of gastrointestinal upset (ie, abdominal pain, nausea, diarrhea, constipation, vomiting, anorexia, and dyspepsia). However, a recent formulation of mycophenolic acid has been shown to be better tolerated. Mycophenolic acid is a delayed-release tablet with an enteric coating, making it ideal for older children who can swallow tablets. Other adverse reactions include leukopenia, pancytopenia, and serious infections. All versions of mycophenolate carry a black box warning for embryofetal toxicities. Women of reproductive age must be counseled regarding pregnancy prevention and planning.

Tremors are not uncommon in patients taking tacrolimus, but rare neurological complications like posterior reversible encephalopathy syndrome can occur with tacrolimus. Other rare but serious complications include thrombotic microangiopathy with calcineurin inhibitors and sirolimus, and oropharyngeal ulcers with calcineurin inhibitors, sirolimus, and mycophenolate mofetil.

Lastly, many medications prescribed by pediatricians, including but not limited to macrolide antibiotics, antifungals, anti-epileptics, antacids, and proton pump inhibitors, interact with immunosuppressive medications. Pomegranate and certain citrus fruits like bitter orange and grapefruit can also cause alteration in the blood levels of immunosuppression medication. It is advisable to consult with the transplant team when prescribing or changing medications. Closer monitoring of levels of immunosuppressive agents may be warranted when changing or adding certain medications.

**FEVER AND INFECTION**

Infections in the posttransplant period may be donor derived, nosocomial, or community acquired. It may be difficult to identify infection in the patient post-transplant because signs or symptoms of infection may be absent or diminished due to the inability to mount an immune response. Additionally, fever may not just represent infection in a patient posttransplant, but could also be a sign of graft rejection or malignancy. All fevers and symptoms of infections should be considered serious in a posttransplant patient, as a large number of pathogens can cause infections in these patients and the infections may progress rapidly.

Most infections in pediatric heart transplant recipients are bacterial in origin, followed by viral, fungal, and protozoal infections, with the highest risk of infection during the first year after transplant. CMV accounts for nearly one-half of the viral infections seen in this population, excluding routine upper respiratory infections and gastroenteritis.

CMV infection may be asymptomatic, but CMV disease can present as fever and neutropenia, lymphadenopathy, pneumonitis, gastrointestinal symptoms (bleeding, gastritis, colitis, ulcers, and pancretatitis), chorioretinitis, or meningoencephalitis. There is some evidence that CMV infection can accelerate development and progression of coronary allograft vasculopathy.

EBV is another common viral infection that may be asymptomatic or at the other extreme cause PTLD. The etiology of PTLD is not completely understood but EBV-induced B-cell proliferation is believed to be a key element. PTLD occurs in 6% of pediatric heart transplant recipients 5 years after transplant.

Infections with polyomaviruses BK and JC are seen in transplant recipients in association with nephropathy. Treatment requires reduction in immunosuppressive drugs. Consultation with a nephrologist is recommended when polyomavirus nephropathy is identified.

The use of prophylactic antibiotics has decreased the incidence of infection with and the resulting mortality of *Pneumocystis jiroveci*. A multi-institutional study showed a prevalence of 1% in pediatric heart transplant recipients in this era of prophylaxis, with the infection commonly seen between 2 months and 2 years after transplant. A mortality rate of 5.5% was reported among the patients who had *P. jiroveci* pneumonia in the same cohort. Data from the same multi-institutional registry showed that invasive fungal infections accounted for approximately 7% of the infections after transplant. The data also demonstrated that most common fungal infections were with *Candida* and *Aspergillus* species. These infections were more common during the first 2 months after transplant.

Infection prevention is key in a transplant recipient. Frequent hand-washing by patients and close contacts should be promoted. Transplant recipients should avoid close contact with those who have symptoms of infections. Dietary counseling, such as consuming only well-cooked meats, washing fruits and vegetables thoroughly (and peeling when appropriate), and avoiding unpasteurized dairy products to prevent infections with *Escherichia coli* or *Listeria monocytogenes* should be provided to the patient and family. Water from wells and lakes should be avoided because it may contain *Cryptosporidium* or *Giardia*.

Often, patients are referred to a primary care physician for fever or infec-
tions. It is important to note that transplant recipients contract infections commonly seen in healthy children and the initial evaluation should include a thorough physical examination to find a focus of infection. Otitis media, upper respiratory infections, and urinary tract infections that present with typical signs and symptoms should be treated similarly to their immune-competent counterparts. Fever or history of fever without a source warrants further evaluation including, but not limited to, blood culture and at least 48 hours of broad-spectrum antibiotics until fever resolves and cultures are negative, or a source for fever is identified. Consultation with the transplant team and an infectious diseases specialist should be considered if there is any question regarding diagnosis and management.

Primary care providers should inform the patient’s transplant team if there are changes in medication(s), if prescribing antimicrobial agent(s) for suspected or proven infections, or if the patient has symptoms such as fever, nausea, abdominal pain, vomiting, diarrhea, blood in stools, poor appetite, unexplained weight loss or weight gain, chest pain, palpitations, dizziness or syncope, or any other unexplained symptoms.

PREGNANCY

Pregnancy in the cardiac transplant recipient is considered high risk but is not absolutely contraindicated. Pregnancy can pose many challenges when complicated by preeclampsia and preterm delivery. There is risk for infection in the recipient during pregnancy as well as at the time of delivery. Pregnancy also places the recipient at risk for acute rejection due to antigens that may be shared by the heart donor and the father of the fetus. In addition, lifelong immunosuppressive medications that are required after transplant have significant teratogenic effects. Due to the high-risk nature of pregnancy after transplant, pregnancy must be meticulously planned with a multidisciplinary team approach including an obstetrician and the transplant cardiologist. Pediatricians must make it a priority to counsel sexually active posttransplant adolescent recipients regarding abstinence or the use of highly effective contraceptive methods at every patient encounter. Contraceptive methods that have a failure rate of <1% should be prescribed. Recipients should be educated that this does not include condoms alone, which have an 18% failure rate. When prescribing contraception, the pediatrician should work closely with the cardiac transplant team.

EXERCISE AND ACTIVITY RESTRICTION

A denervated graft does not have the normal chronotropic response to exercise. Therefore, a child with a newly transplanted heart has a higher resting heart rate (HR) but will have a slow increase in HR and reduction in peak HR during exercise, with slower return to baseline after exercise. There is clear evidence of benefit from regular aerobic activity in heart transplant recipients. A randomized controlled trial involving heart transplant recipients demonstrated improved exercise capacity in transplant recipients who participated in a high-intensity interval training program. This trial demonstrates the safety and benefit of regular aerobic activity in this population. Moreover, there is evidence that metabolic syndrome, largely a result of sedentary lifestyle, contributes to the development and progression of coronary allograft vasculopathy. The absence of data in literature with regard to exercise-related cardiac events in cardiac transplant recipients could be because either transplant vasculopathy is not associated with the same risks as atherosclerosis or because too few transplant patients participate in competitive sports to generate data. As such, the American Heart Association has put forth some recommendations. An annual exercise stress test can be obtained that simulates the metabolic demands of the competitive event prior to participation. The guidelines state that “it is reasonable for cardiac transplant recipients with an ejection fraction >50%, no evidence of cardiac ischemia, and no electrical instability to participate in all competitive activities commensurate with their exercise tolerance.” The transplant cardiologist should make the final decision regarding sports participation in this population.

Similarly, patients who have developed mitral or tricuspid valve regurgitation secondary to rejection or graft dysfunction may also undergo an exercise stress test prior to sports participation. However, they need not be restricted from recreational sports and physical education class at school as long as they are allowed to stop and seek help if they develop symptoms. It is imperative upon the health care team to encourage physical activity in this patient population unless there are strong reasons to restrict.

LIFE IN THE SHOES OF A PEDIATRIC HEART TRANSPLANT RECIPIENT

Although the goal of cardiac transplantation is to increase the duration and quality of the life of the recipient, transplantation remains a substitution of one chronic health problem for another. Early post-cardiac transplant management can be extremely challenging for recipients and their families. Weekly clinic visits, polypharmacy, cardiac catheterizations, and frequent laboratory blood draws place a significant burden on the patient and family immediately
after transplant. Coordination of care by the transplant team is imperative for a successful posttransplant discharge. Patients and families may struggle early after transplant with noncompliance or nonadherence to the posttransplant medical management, placing the recipient at increased risk for mortality. Studies describing quality of life (QoL) of pediatric cardiac transplant recipients have reported improved QoL, but not without complications. School-age and adolescent recipients have reported feeling happy about being able to participate in activities with friends and being thankful for the organ donor; however, these same recipients were resentful about the pain suffered from blood draws, biopsies, medication side effects, and changes in body image. Parents of pediatric cardiac transplant recipients have reported significant improvements in the child’s physical condition after transplant, but they also reported feeling anxious, constantly worried, and responsible for the child’s well-being. They also reported that postcardiac transplant management remained a constant controlling factor in their lives. Due to the many challenges faced by postcardiac transplant recipients and their families, it is imperative for the pediatrician to work closely with the recipient family and the cardiac transplant team to assure successful posttransplant outcomes.

REFERENCES


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