6 Pediatric Cardiac Transplantation and Mechanical Assist Devices

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Introduction

The number of heart transplant candidates who are listed and the number performed in children has been steadily increasing in the United States. In 2015, the number of new pediatric candidates added to the waiting list was 644, the highest number to date. There were 460 pediatric transplants performed, 16% of the total number of heart transplants in the United States, compared to 297 in 2004 [1]. Heart transplantation is the best option for children with end-stage heart disease. In the recent era, overall 1-year and 5-year survivals are 90.7% and 81.4%, respectively [2]. Improvement in perioperative management has accounted for the improved survival over the eras (Fig. 6.1). The use of mechanical assist devices has also increased tremendously over the years. Patients with a ventricular assist device (VAD) at the time of transplant have tripled from 8.8% in 2002–2005 to 24.6% in 2012–2015 [1]. There are no large, randomized, controlled trials in the management of end-stage heart disease, use of mechanical assist devices, or heart transplantation management in pediatrics. In many instances, the heterogeneous nature of the pediatric heart failure population and the small numbers relative to adult patient populations make this type of study impractical. As with other areas of pediatric medicine, we often extrapolate from adult clinical trials, large pediatric registry data, and single-center studies. We aim to discuss the current use and challenges with mechanical assist devices in the pediatric population. We will also look at some contemporary issues in pediatric heart transplantation such as immunosuppression, retransplantation, and rejection surveillance.

Overview of Mechanical Assist Devices

In 2006, there were nearly 1,400 heart failure hospitalizations in children [3]. Heart failure-related intensive care mortality in patients with cardiomyopathy has been reported at 11% [4]. When comparing patients with cardiomyopathy, mean length of stay for heart failure admission in children is significantly longer than in adults,

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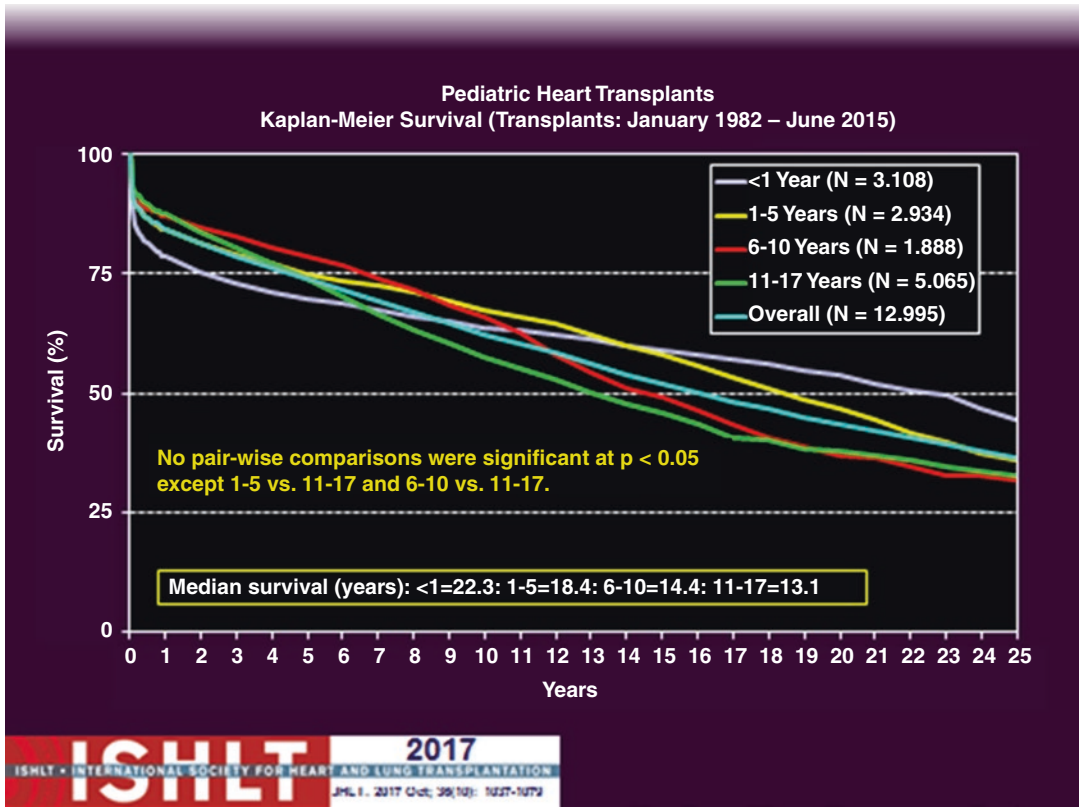


Fig. 6.1 Kaplan-Meier survival of pediatric heart transplants performed between Jan. 1982 and June 2015. Since many patients are still alive and some patients have been lost to follow-up, the survival rates are estimates rather than exact rates because the time of death is not known for all patients. The median survival is the estimated time point at which 50% of all of the recipients have died

16 days versus 7 days, respectively [5]. The differences in length of stay are likely related, at least in part, to the disparity in out-of-hospital options for young children as compared to adults. For instance, there are limited mechanical assist device options for children that would allow for discharged home. Although mortality rates for both pediatrics and adults with cardiomyopathy have decreased over time, overall mortality is worse in children. Infants have the highest mortality rate of any age group, including patients greater than 70 years of age [5].

The prevalence of children born with congenital heart disease worldwide is approximately 1% [6]. Advances in surgical technique in infants with congenital heart disease have palliated patients that would have otherwise died in earlier eras, but a significant proportion of these patients will develop end-stage heart failure that require heart transplantation [7]. As is the case in all solid organ transplantation, the demand for organs exceeds the supply. So, although transplant remains the best treatment option for children with end-stage heart failure, waitlist mortality remains an issue. Mechanical circulatory support provides a temporary solution to the shortage of donor hearts [8]. In the adult population, there has been significant investment by industry in the research and development of ventricular assist devices. These devices have revolutionized the treatment of advanced heart failure in adults [9]. The field of mechanical circulatory support in children has lagged behind but in the recent era has made great strides.

Pediatric Ventricular Assist Devices

ECMO

Extracorporeal membrane oxygenation (ECMO) is a method of support in which the device completely supports circulation and gas exchange. The device is commonly employed for patients with heart or respiratory failure. Depending on the indication for its use, it can be veno-venous for purely respiratory support or venoarterial for cardiorespiratory support. The contemporary ECMO circuit is composed of a centrifugal pump, a membrane oxygenator, and a heater/cooler device. Cannulas connecting the device to the patient are usually implanted into peripheral blood vessels either via surgical cutdown or percutaneously. In neonates and infants, the usual route of cannulation is via the right cervical vessels. A cutdown is made over the right lateral aspect of the neck and the carotid artery and jugular vein are then used as insertion sites for cannulas that allow inflow and outflow from the device. ECMO can also be implanted from the femoral vessels if size allows or via central cannulation for patients in postcardiotomy shock. One advantage of ECMO is that it is rapidly deployable at the bedside, allowing for salvage of critically ill patients, sometimes after cardiac arrest with cardiopulmonary resuscitation (CPR) in progress. Since ECMO cannulas can be introduced peripherally, sternotomy is avoided in these patients, simplifying subsequent operations.

ECMO support carries significant risk of morbidity and mortality that worsens as support time increases. In the Berlin Heart EXCOR Investigation Device Exemption (IDE) trial, the Extracorporeal Life Support Organization (ELSO) registry was used for historical controls. Patients were divided into two cohorts based on body surface area (BSA). No patient with a BSA < 0.7 m^2 survived longer than 21 days on ECMO, and in patients with a BSA 0.7–1.5 m^2, survival approached zero at 28 days [10]. This study highlights the unsuitability of ECMO as a long-term support strategy. ECMO should therefore be restricted to short-term (<30 days) support as a bridge to recovery, transplantation, or implant of a more durable ventricular assist device.

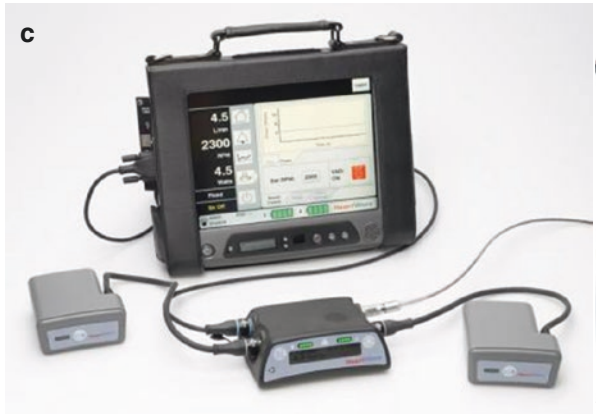
Berlin Heart

The Berlin Heart EXCOR is the only dedicated pediatric VAD that is approved for use as bridge to transplantation (Fig. 6.2a). The Berlin Heart EXCOR is paracorporeal and a pneumatically driven pulsatile ventricular assist device that can be used to support the left, right, or both ventricles. The VAD is made in a variety of sizes for use in infants, children, and adolescents. Typically the 10, 15, and 25 ml devices are used in infants and small children given that larger children are candidates for continuous-flow devices designed for use in adults with a much better side effect profile [11]. The Berlin Heart EXCOR has proven to be to be superior to ECMO support for end-stage heart failure in children. The device however is associated with significant morbidity that includes bleeding, infection, and stroke. The use of the Berlin Heart EXCOR carries an almost 30% risk of stroke with varying degrees of neurologic dysfunction [10]. Patients often require multiple pump exchanges due to thrombus formation inside the device, incurring significant cost.

Paracorporeal Centrifugal Pumps (CentriMag, PediMag)

The CentriMag and PediMag are extracorporeal blood pumps that can provide complete hemodynamic support in adults and children (Fig. 6.2b). The pumps have fully magnetically levitated rotors that minimize blood-related complications such as hemolysis. The CentriMag is designed for use in patients that are greater than 20 kg. The PediMag pump is of similar design but optimized to provide support for children that are less than 20 kg. These devices are cleared by the FDA for use in acute support situations for either ventricle (6 h) or as a right ventricular assist device (RVAD) for up to 30 days. Despite the current FDA-approved indications, these pumps are routinely

Fig. 6.2 Mechanical assist devices. (**a**) Berlin Heart EXCOR biventricular support and console with varying sizes of pumps. (**b**) PediMag device and console. (**c**) HeartWare HVAD console and pump. (**d**) Thoratec HeartMate II LVAD. (**e**) HeartMate 3 LVAD



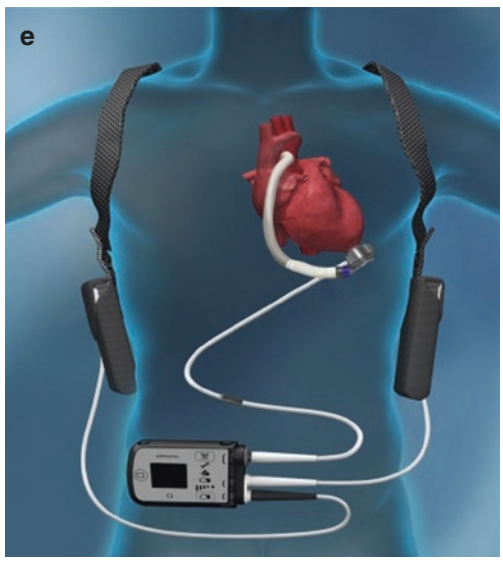


Fig. 6.2 (continued)

used off label for much longer periods as part of the ECMO circuit or as paracorporeal ventricular assist devices. Some centers, in an effort to reduce the cost associated with frequent pump exchanges often required with the Berlin Heart EXCOR, use these continuous-flow devices as an alternative. Use of the CentriMag and PediMag devices connected via Berlin heart cannulas has been described in small case series [12–14].

HeartWare HVAD

The HeartWare HVAD is a fully implantable, continuous centrifugal flow device (Fig. 6.2c). The pump's only moving part is a magnetically stabilized rotor. A single drive line exits the body and connects to an external controller device and batteries. There are no mechanical bearings making it highly durable. The device has been extensively used as bridge to transplant in adults and has recently been approved for destination therapy [15]. Given the better side effect profile associated with continuous-flow devices versus older pulsatile flow pumps, the HVAD is preferred to the Berlin Heart EXCOR in larger children. Though designed to be used in adult patients, the use of the HeartWare HVAD is possible in children with BSA greater than 0.6 m^2 with modifications to the implant technique (i.e., preperitoneal pocket vs. intra-pericardial) [16]. Patients and their guardians can be trained in the day-to-day management of the HVAD. Children supported with this device have been able to go to school and lead a relatively normal life while waiting for heart transplantation.

Thoratec HeartMate II

The Thoratec HeartMate II LVAD is a fully implantable left ventricular assist device approved for use as both bridge to transplant and destination therapy (Fig. 6.2d). The device features an axial rotor supported by ruby bearings and can provide up to 10 liters of blood flow per minute. The HeartMate II has been approved for use in adults since 2008 and has been implanted in over 20,000 patients. In the adult population, the HeartMate II has been shown to improve both survival and quality of life with an improved side effect profile, when compared to older pulsatile designs [7]. The device is implanted via a median sternotomy and placed in a surgically created preperitoneal pocket. A single drive line exits the abdomen and connects the device controller and batteries. Due to its size, this device can only be used in adult-sized patients (BSA greater than 1). Despite the decreased incidence of adverse events compared to older, pulsatile devices, there are still significant issues with morbidity associated with this device including stroke, gastrointestinal bleeding, intractable drive line infections and pump thrombosis [17].

Thoratec HeartMate 3

The HeartMate 3 LVAS (left ventricular assist system) is the most recent ventricular assist device approved for use as bridge to transplant (Fig. 6.2e). The device, which features a completely magnetically levitated rotor that provides wide spaces for blood flow, is designed for improved hemocompatibility and reduced pump-related morbidity. The HeartMate 3 has proven to be highly resistant to pump thrombosis. Its design and reduced size makes it easier to implant [18, 19]. Given its proven benefits and recent approval as bridge to transplant, the HeartMate 3 is our device of choice in the adolescent population. The HeartMate 3 is larger than the HeartWare HVAD, which may make implant in smaller children more challenging.

Decision-Making in Pediatric Mechanical Support

Adequate decision-making plays a significant role in mechanical circulatory support. Despite recent advances in technology, the use of invasive devices is associated with significant morbidity and mortality and must be weighed against continued medical management with potential further deterioration and end organ damage [9]. In

the adult population, given the availability of newer-generation devices with a more favorable side effect profile, the decision to proceed with VAD implant is simplified. In the current era, continued medical management in the setting of worsening functional status and end organ dysfunction is no longer indicated and, furthermore, is associated with worse outcomes even if implant of a VAD is eventually undertaken. Dependence on intravenous inotropic support is the usual indication that prompts VAD implantation. There are, of course, some exceptions to this rule, such as favorable blood type with short transplant wait times in the bridge-to-transplant patient.

In pediatrics, the decision to proceed with VAD implantation is complicated by several factors including patient size, device availability, blood type, expected transplant wait time, etiology of heart failure, and overall condition of the patient. There is significant variability in practice across the world that considers the abovementioned factors with no approach being supported by evidence. Decisions on the use of mechanical support in the pediatric patient with heart failure must therefore be based on physician experience and sound physiologic rationale.

Patient Size

Small Children (BSA < 0.6 m^2)

There are limited mechanical support options for small children in heart failure [20]. ECMO is commonly used in conjunction with CPR (ECPR) or when short duration of support is anticipated. Long-term mechanical support options currently available are the Berlin Heart EXCOR and the PediMag LVAD connected to Berlin Heart cannulas. Due to the limited options and high morbidity associated with mechanical support in small children, we seek to minimize the child's exposure to a device as long as it is reasonable to do so. In children who are less than 5 kg, every attempt is made to delay VAD implantation. Pulmonary artery banding has been reported as a temporizing measure for patients with dilated cardiomyopathy with preserved right ventricular function [21]. Banding the pulmonary artery will increase the right ventricular pressure and shift the interventricular septum leftward. This reconfiguration of the septum can reduce mitral regurgitation by reducing mitral valve annulus diameter and reportedly improve cardiac output. Pulmonary artery banding in very small children with dilated cardiomyopathy may be an acceptable alternative to VAD allowing the child to grow to sufficient size for a safer VAD implantation or to be transplanted [21].

A comprehensive evaluation to rule out reversible causes of heart failure accompanied by multidisciplinary management discussions should take place for every child admitted in heart failure. If deterioration progresses despite inotropic support, mechanical ventilation is the next step in escalation of care. Intubation should be done in a controlled setting with surgical consultation immediately available should ECPR need to be deployed. It is not uncommon for a child whose status is deteriorating to arrest while attempting intubation. In this scenario, ECPR with prompt restoration of cardiac output can be lifesaving [22]. Mechanical ventilatory support decreases cardiac preload and afterload in the failing heart and also reduces the effort made by a child with limited cardiopulmonary reserve [23]. Ventilator dependence should trigger VAD implantation, with the goal of liberation from mechanical ventilation. Long-term mechanical ventilation and its required sedation cause progressive deconditioning, which can affect posttransplant outcomes. Being on mechanical ventilation is a known risk factor for poor outcome after heart transplantation [24, 25]. Successfully implanting a durable VAD that restores adequate cardiac output and allows the patient to be mobilized, rehabilitate, and gain weight is worthwhile despite the risks of surgery.

Right heart catheterization can be helpful in assessing the right heart function prior to implantation but should be weighed against the risk. Echocardiographic evaluation of the right heart can often lead to concerns of post-VAD implant right heart failure. Because of high left-sided filling pressures and high pulmonary artery pressures, the right heart can appear to be severely

dysfunctional. Once the LVAD is implanted and the filling pressures of the left ventricle improve, often what appeared to be a failing right ventricle can provide adequate cardiac output to fill the left-sided device. There is evidence that the use of biventricular VADs (BiVADs) is associated with worse outcomes [26]. Avoidance of biventricular support at all costs however is also ill advised. A child struggling in low cardiac output due to RV failure after VAD implantation can develop worsening end organ dysfunction. With the Berlin EXCOR, evidence of LVAD under filling, low cardiac output, and high right-sided filling pressures should prompt RVAD implant as soon as possible. Under filling of the left-sided device also causes wrinkles to form on the pump diaphragm, providing a nidus for clot formation even if anticoagulation is adequate. Clot formation increases the risk of embolus and its associated neurologic and vascular complications.

When right heart function is marginal, under filling of the Berlin Heart EXCOR can occur, increasing the risk of pump thrombosis and its associated morbidities including stroke. For this reason, some centers will implant the Berlin Heart EXCOR cannulas in the usual fashion and connect a PediMag continuous-flow pump instead of the pulsatile Berlin Heart EXCOR when RV dysfunction is present. This approach allows the patient to recover from the initial postoperative right ventricular dysfunction without the associated risk of an under-filled Berlin Heart EXCOR device. Once the child is extubated, the marginal right ventricular function usually improves, allowing for the patient to be transitioned to a Berlin Heart EXCOR device for long-term support. It is important to note that this approach requires close monitoring for progressive right ventricular dysfunction. Marginal LVAD flows with evidence of end organ dysfunction in the setting of right ventricular dysfunction should prompt RVAD implant before further clinical deterioration ensues.

Key points in small children (BSA < 0.6 m²):

- *VAD team evaluation once inotropic support is started.*
- *VAD implant if ventilator dependent.*
- *Avoid BiVAD implant if possible.*
- *Do not delay in RVAD implant if evidence of right heart dysfunction develops post LVAD implant.*

Larger Children (BSA > 0.6 m²)

Children whose body surface area is >0.6 m² become candidates for the HeartWare HVAD. This device, as described above, is designed for use in adults and approved for long-term support. In adults, the HVAD has a significantly better side effect profile than older paracorporeal pulsatile devices that are designed similar to the Berlin Heart EXCOR [11]. In pediatrics, there has been great interest in using continuous-flow devices in the hope of replicating the results seen in adults. There is currently little evidence to support using implantable continuous-flow devices rather than the Berlin Heart EXCOR, but given the reduced incidence of adverse events reported in the adult literature, many centers favor VAD implant earlier in the disease course [27]. It is our practice to consider implant of the HeartWare HVAD in larger children as soon as the child becomes dependent on one or more positive inotropic drugs (e.g., milrinone, dobutamine, etc.). Regional wait times, blood type, and overall condition of the patient will factor into the decision to implant the device or to continue to wait for transplant on inotropic infusions. Restoration of adequate cardiac output before the onset of end organ dysfunction has been shown to improve VAD outcomes in adults. The HeartWare HVAD is connected via a single drive line to a small controller and batteries. This design makes it possible for patients to resume many normal activities that improve the physical and psychological condition of the child. Implant of the HVAD is not free of the complications that affect all newer-generation continuous-flow devices such as drive line infections, gastrointestinal bleeding, and stroke. Despite these possible complications, it is thought that the benefits of earlier VAD support outweigh these concerns. It is not inconceivable that as VAD technology improves and adverse effects decrease, VAD

implant will become an option for patients who are in significant heart failure but not yet inotrope dependent.

Adult-sized adolescents can be implanted with any VAD currently on the market. The HeartMate 3 device was recently approved as a bridge-to-transplant device. The HeartMate 3 device has been designed for improved hemocompatibility in an effort to reduce adverse events. The device has been widely used in Europe and has been implanted may times in the United States as part of the Momentum 3 trial [18]. In both the European and US experience with this device, there has been a dramatic reduction in pump thrombosis and need for pump exchange. Pump thrombus has been a significant source of morbidity and mortality in patients supported on VADs. The resistance to thrombosis demonstrated by the HeartMate 3 LVAD opens up exciting possibilities for future changes in the anticoagulation management that will hopefully decrease the rate of bleeding complications. FDA approval of the HeartMate 3 makes it our device of choice in adult-sized adolescents over the older HeartMate II.

Key points in larger children (BSA > 0.6 m^2):

- *Implant when patient is dependent on inotropic infusions.*
- *Use centrifugal continuous-flow devices.*
- *HeartMate 3 preferred device when the child's BSA is greater than 1 (i.e., adult size) due to its relative resistance to pump thrombosis.*
- *May discharge home on VAD support with adequate patient and caregiver education.*

Anticipated Duration of Support

Bridge to Recovery

Heart failure due to a potentially reversible etiology, like viral myocarditis or arrhythmia-induced cardiomyopathy, is often treated with mechanical support once medical management becomes untenable. ECMO support provides adequate short-term support and avoids more invasive options. In patients with surgically correctable conditions, central ECMO cannulation for post-cardiotomy shock avoids cannulating the ventricle as is frequently necessary for VAD implant. If a reasonable period of time (1–2 weeks) has passed with little evidence of recovery, then alternate, longer-term support options should be discussed. Conversion to a long-term VAD while awaiting transplant will depend on the anticipated wait time on the heart transplant list. Centers must take regional and patient-specific factors into account when deciding when to abandon the short-term support strategy in favor of a longer-term device.

Bridge to Transplant

In patients whose heart failure etiology is unlikely to recover, VAD implantation is done as a bridge to transplantation. The benefits of VAD support while awaiting transplant are significant in both the adult and pediatric population [28]. A common scenario is a child with heart failure who acutely deteriorates and requires emergent ECMO cannulation or ECPR. Once the child is hemodynamically stable on ECMO and recovery of end organ dysfunction has been proven, the decision between waiting for heart transplantation on ECMO and transitioning the patient to a more durable VAD must be made. The decision will depend on several factors. Blood type can significantly affect wait times. If the child is a candidate for ABO-incompatible heart transplant or if the blood type is AB, which are associated with the shorter wait times in some regions, it may be reasonable to avoid the insult of VAD implant. Wait times also vary widely by geography, and because listing across blood groups in infants is an accepted practice, listing across blood groups does not necessarily shorten waitlist times. It is important to be familiar with the local organ procurement organization (OPO) to assist with decision-making and estimate wait times. If the anticipated wait time is greater than several weeks, it is reasonable to transition the patient to a durable VAD.

Once the VAD is implanted, the physiological impact of the procedure must be evaluated to

decide when to activate the patient on the transplant list. Some centers will inactivate recently implanted patients for several weeks to wait for recovery. We believe that the decision to make a recently implanted patient active on the transplant list must be made on a case-by-case basis. In a small child recently implanted with a Berlin Heart, who is doing well several days post implant with no evidence of end organ dysfunction, significant inflammation, or fluid retention, it is reasonable to proceed with transplant if an adequate heart becomes available. The risk of continued exposure to the VAD should be weighed against the risk of performing a heart transplant on a debilitated patient who has just undergone a major operation. In older patients who have been implanted with a continuous-flow device, it is reasonable to wait a longer period before reactivation on the transplant list. The lower risk of adverse events with newer continuous-flow devices shifts the risk/benefit analysis toward waiting for the patient to recover and transition from a catabolic to an anabolic state.

Destination Therapy

In patients who are not candidates for transplantation but are suffering from heart failure, there are several devices that are FDA approved for long-term support. In the pediatric population, destination therapy is not a common indication for implant. There are several reports of implants in patients with progressive degenerative conditions that disqualify them for heart transplant [29, 30]. These cases have so far been the exception rather than the rule. We expect that as device technology improves, destination therapy may become a viable alternative to heart transplantation in pediatric patients.

Special Circumstances

Ventricular Assist Device Therapy in Functional Single Ventricles

There has been limited enthusiasm for VAD therapy as bridge to transplant in single-ventricle patients in various stages of palliation. Studies have shown dismal outcomes when single-ventricle patients with shunt physiology undergo VAD therapy, with slightly better results in patients that have undergone second and third stage of the single-ventricle palliation [31]. Given the available evidence, we would not offer VAD therapy to a single ventricle before the last stage of palliation. In these cases, we would support the patient with ECMO as bridge to transplant. In patients with failure of the Fontan circulation, if VAD therapy is being considered, it is critical to determine the mechanism of failure. Cardiac catheterization should be performed to document the ventricular filling pressure and confirm anatomy. If the patient has failed Fontan physiology with normal ventricular filling pressure, a VAD implant is unlikely to improve outcomes and the patient should be transplanted. If there is high ventricular filling pressure, then a VAD may improve the patient's symptoms [32].

There are other risk factors and comorbidities that have to be considered when considering VAD placement in a Fontan patient as a bridge to transplant. Multiple sternotomies cause significant scar formation that can make the operation technically challenging. Patients with failing Fontan physiology are also commonly debilitated by protein-losing enteropathy and have limited immunologic and hepatic reserve to tolerate the insult of a major operation. Due to these potentially complicating factors, VAD therapy has not become commonplace as a bridge to transplant in this population, even if there is objective evidence of possible benefit. Multidisciplinary evaluation that includes cardiology, cardiac surgery, hepatology, and anesthesia should be completed before any surgical procedure is undertaken.

Anticoagulation After VAD Implant

Management of anticoagulation while on mechanical support is a critical component to achieve good outcomes and avoid complications [33]. In older children implanted with continuous-flow devices, the anticoagulation strategy is similar to the adult patient. A heparin infusion is started 24–48 hours post implant after

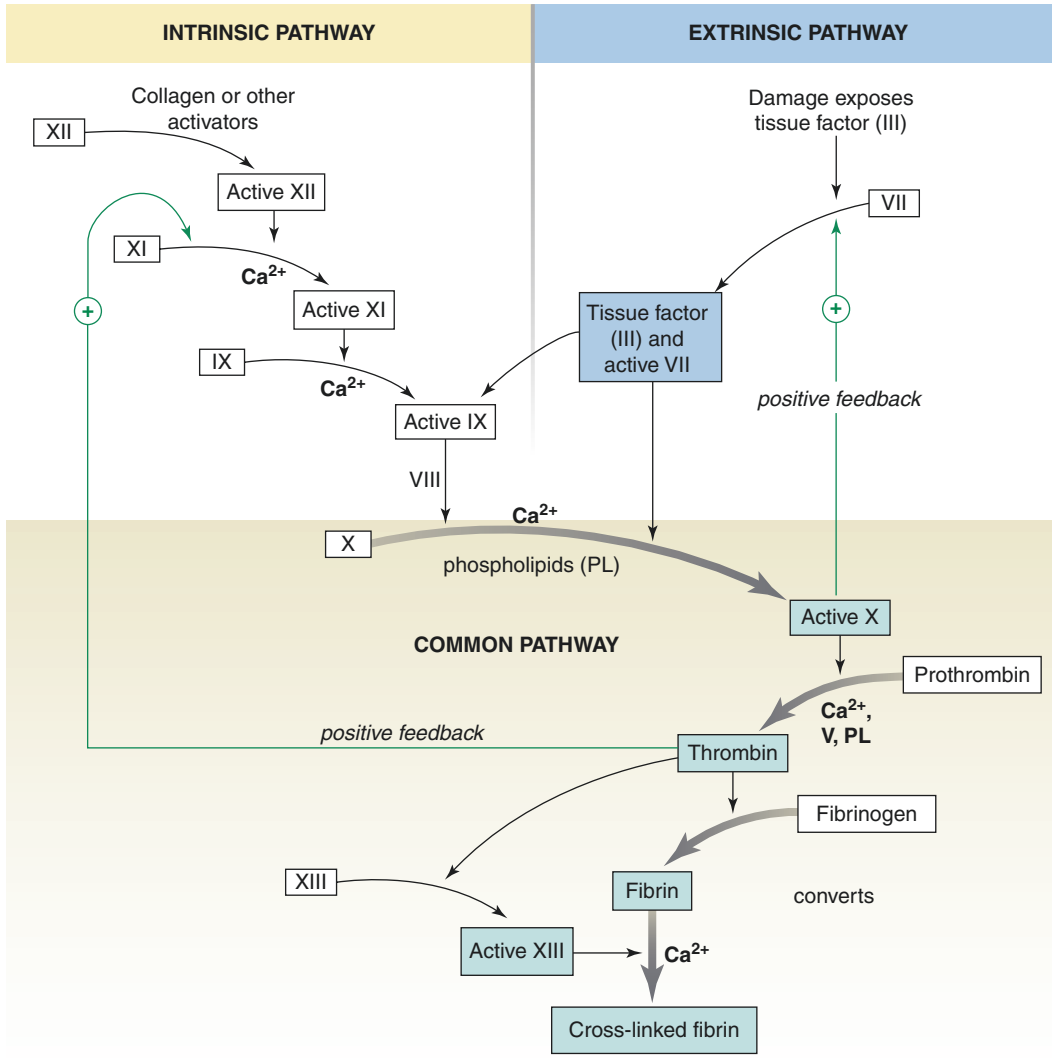


Fig. 6.3 Clotting cascade

postoperative bleeding resolves. Heparin binds to the enzyme inhibitor antithrombin III which then inactivates thrombin and factor Xa. Aspirin is started 48–72 hours after the patient returns from the operating room. Aspirin irreversibly blocks the formation of thromboxane A2 in platelets preventing platelet aggregation for the life of the affected platelet. Warfarin is then started in preparation for discharge once the patient is tolerating a regular diet. The international normalized ratio (INR) goal is 2–3. Warfarin inhibits the synthesis of clotting factors II, VII, IX, and X in addition to regulatory factors, proteins C and S (Fig. 6.3).

Smaller children supported with the EXCOR device are especially prone to embolic complications primarily because the pumps must be run at lower rates. Lower flow through the device makes thrombus formation more likely. In this high-risk population, management of anticoagulation postoperatively is especially important. In young patients, anticoagulation is challenging for a variety of reasons. Hemostasis is a complex process involving many proteins, and the level of proteins

involved in hemostasis changes significantly with age. An example of this variation is the enzyme inhibitor antithrombin III (AT3). In children, normal AT3 levels are less than 50% of adult levels. This relative AT3 deficiency can pose a challenge, given that AT3 is the pharmacologic target of heparin, the most commonly used anticoagulant for VAD patients both intra- and postoperatively. Because of these developmental variations in hemostasis, clotting and bleeding can be unpredictable.

Once anticoagulation is started, monitoring practices vary widely. Many tests are often ordered with sometimes contradictory results. Adding to the difficulty, it is unclear what value of a given test indicates adequate anticoagulation therapy in the pediatric population [34]. Early in the Berlin Heart IDE EXCOR trial, a protocol was put in place to standardize the management of the anticoagulation across all patients in the trial (Tables 6.1 and 6.2). Referred to as the Edmonton protocol, it is still the standard for the management of anticoagulation for patients on the EXCOR VAD [33]. Despite the use of a standardized anticoagulation protocol, the Berlin Heart IDE trial had very high rates of stroke, pump thrombosis, and bleeding. These complications are related to multiple patient and device factors including size and design of the pump. Surgeons depend on heparin anticoagulation for cardiopulmonary bypass and are therefore familiar with the drug and comfortable with its use in children. Unfractionated heparin has important downsides when used in the pediatric patient. The reason heparin is called unfractionated is because it has molecules of varying sizes in a single vial. Because of the variable molecular size, there is variable activity of the molecule against thrombin and factor Xa. The amount of the 18-saccharide unit that is active and binds to AT3 is variable. Heparin also has a propensity to adhere to positively charged plasma proteins that can alter the bioavailability of the drug. All these factors make for a nonlinear response to heparin dosing. Chronic exposure to heparin also causes osteopenia in already debilitated children and, although less common than in adults, can cause heparin-induced thrombocytopenia (HIT) [35, 36].

The challenges that arise when using heparin as the principal drug in an anticoagulation regimen have prompted some in the field of pediatric heart failure and mechanical support to try alternate strategies with more predictable drugs. VanderPluym et al. have championed the use of direct thrombin inhibitors in mechanically supported children [36]. The ideal alternate to heparin would be a drug that is reliable, with highly predictable dosing, fast onset, and a short half-life. Ideally, the drug would not require other factors or plasma proteins to get the job done and would not be impacted by renal or hepatic dysfunction. Direct thrombin inhibitors meet most if not all of these requirements. The most commonly used direct thrombin inhibitor in mechanically

Table 6.1 Edmonton antiplatelet protocol for Berlin Heart EXCOR

	Initiation parameters	Goal antiplatelet
>48 hrs	Plt > 40,000 ADP inhibition <70% MAckh>56 mm	Start dipyridamole (4 mg/kg/day divided in 4 doses) titrate to TEG ADP inhibition
4–7 days	All drains removed AA inhibition <70% MAckh >72 mm	Start ASA (1 mg/kg/day divided in 2 doses) titrate to TEG AA inhibition

Plt platelets, *ADP* thromboelastography adenosine diphosphate pathway, *AA* thromboelastography arachidonic acid pathway, *MAckh* maximum amplitude, citrated blood sample activated with kaolin and heparinase, *ASA* acetylsalicylic acid; aspirin

Table 6.2 Edmonton anticoagulation protocol for Berlin Heart EXCOR

	Initiation parameters	Goal anticoagulation
24–48 hrs	Plt > 20,000, TEG MA > 46	Start UFH, goal anti-Xa 0.35–0.5
2–4 days	No bleeding, normal renal function	Transition Lo LMWH eventual anti-Xa 0.6–1
>1 week	>12 months old, no bleeding, tolerating enteral feeding	Warfarin with goal INR 2.7–3.5 bridge with LMWH if INR < 2.7

Plt platelets, *MA* maximum amplitude, *TEG* thromboelastography, *UFH* unfractionated heparin, *LMHW* low molecular weight heparin, *INR* international normalized ratio

supported children has been bivalirudin. Bivalirudin directly inhibits thrombin, which in turn is responsible for cleaving fibrinogen into fibrin and activating factor XIII, which stabilizes a thrombus by fibrin cross-linking. Bivalirudin has linear pharmacokinetics, with a dose- and concentration-dependent activity in prolonging the activated clotting time (ACT), activated partial thromboplastin time (aPTT), prothrombin time (PT), and thrombin time. It has quick onset with almost immediate effect and does not bind to plasma proteins. Bivalirudin does not depend on AT3. The drug is also metabolized by proteolysis and less than 20% of it is excreted by the kidney. The half-life of the drug is 25 min, which mitigates some of the concern about the lack of antidote. In the case of significant bleeding or prior to a procedure, turning off the infusion is usually sufficient for reversal of anticoagulation. Like all drugs however, bivalirudin has several associated risks. Renal dysfunction will increase its half-life. When on bivalirudin, blood stasis must be avoided; proteolysis will degrade the drug in static blood and allow clotting. If a procedure in which stasis is expected such as a pump weaning trial, transition to heparin anticoagulation should be strongly considered. For unclear reasons, chronic use of bivalirudin requires increasing the dose over time. Although there is no antidote for the drug, fresh frozen plasma (FFP) and activated factor VIIa may be used if life-threatening bleeding were to occur. The need to reverse bivalirudin acutely is rarely necessary due to its short half-life, though half-life will be prolonged in patients with severe renal dysfunction. Importantly, bivalirudin is dialyzable.

There is experience in using bivalirudin in mechanically supported children. Bivalirudin has been used successfully in children on ECMO when there is concern for HIT and when anticoagulation with heparin becomes difficult, which can be indicated by increasing doses to maintain adequate anticoagulation or the need for multiple doses of AT3. In some published series, the use of bivalirudin on ECMO has shown no difference in rates of thromboembolism or bleeding compared to heparin [37]. The drug has also been used successfully during cardiopulmonary bypass for adults and children with HIT [38–40]. Experience with the use of bivalirudin with the EXCOR is limited but so far encouraging. Rutledge et al. reported six patients supported with the Berlin Heart EXCOR. These patients were switched to bivalirudin due to heparin-associated complications including HIT and pump thrombosis. In this small series, one patient had a stroke with complete recovery. The rest of the patients had no complications while on the drug and five were successfully transplanted [41]. Studies are actively underway to definitively confirm the superiority of direct thrombin inhibitors over the Edmonton protocol. There is currently no set pediatric dosing for bivalirudin in these clinical scenarios. The Boston group recommends a bolus (0.1–0.2 mg/kg) if urgent increase in anticoagulation is needed followed by ACT measurement [36]. If the ACT is greater than 225 seconds following the bolus, an infusion is started at 0.15–0.5 mg/kg/hr, always starting at lower doses in patients with renal dysfunction. Once bivalirudin is initiated, therapy is titrated based on aPTT measurements, with target levels of 1.5–3 times that of baseline measurements, depending of the patient's individual risk of bleeding (e.g., within the early postoperative period, abnormal platelet function) versus clotting risk (e.g., fibrin visible in the pump, systemic infection with increased inflammation). All bleeding must stop in the early postoperative period before starting bivalirudin. Once the infusion is started, an aPTT is measured. The aPTT is also measured every 4 h after dose change. Checking daily aPTT and INR is recommended, in addition to weekly thromboelastography (TEG) with platelet mapping, lactate dehydrogenase, C-reactive protein, and full coagulation studies (Table 6.3) [36].

Heart Transplantation

Early posttransplant survival has improved over the eras. Infant and adolescent median survivals are 22.3 and 13.1 years, respectively (Fig. 6.1). Patients who survive the first year after transplant have a median survival of 15 years in all age groups [2]. As survival improves, the focus in

Table 6.3 VanderPluym et al.'s recommendations for starting and titrating bivalirudin

Bivalirudin dosing	Starting bolus	Starting infusion dose
	0.1–0.2 mg/kg	0.15–0.5 mg/kg/hr
Bivalirudin monitoring and titration		
aPTT results	**Adjustment**	
1–15 seconds out of target range	+/−0.2 mg/kg/hr. from initial infusion rate	
16–30 seconds outside of target range	+/− 0.5 mg/kg/hr. from initial infusion rate	

VanderPluym [36]

pediatric transplant medicine can change to find ways to enhance long-term survival and improve quality of life by decreasing the morbidity that is inherent with this therapeutic modality.

Immunosuppression

Immunosuppression is the mainstay of transplantation management, but each of the drugs used can have adverse effects (Table 6.4). Combinations of drugs that have evolved over the years have decreased the incidence of rejection while minimizing toxicity by avoiding the need to use high doses of any single drug. However, it is difficult to say which regimen is ideal due to lack of pediatric randomized, controlled trials. Without such trials, we cannot adequately account for selection bias and the numerous covariates that affect transplant outcomes. Clinical practice has changed over the years as newer drugs that are more immunosuppressive with less cosmetic side effects or that target different inhibitory pathways of T- and B-cell replication have become available. The 2017 International Society for Heart and Lung Transplantation (ISHLT) registry report shows that over the eras, cyclosporine and azathioprine use has decreased, while tacrolimus and mycophenolate mofetil (MMF) use has increased. Similarly, as more pediatric studies suggest that induction therapy may decrease risk of early rejection while not increasing the risk for infection and malignancy, its use in clinical practice has changed [42, 43]. In the recent era, 70% of pediatric heart transplant recipients received some form of induction therapy with the majority of patients receiving anti-thymocyte globulin. Despite the changes in clinical practice, no survival benefit has been shown with any of these changes [2].

Table 6.4 Adverse effects of immunosuppression

Drug	Adverse effects
Tacrolimus	Hyperkalemia, hypomagnesemia, hyperglycemia, metabolic acidosis, elevated transaminases, nephrotoxicity, tremors, hypertension, headaches, leg cramps, hair loss
Mycophenolate	Myelosuppression, gastrointestinal side effects, headaches, viral reactivation infections (CMV, EBV), lymphoma, pregnancy loss, and fetal malformations
Cyclosporine	Hyperkalemia, hypomagnesemia, hyperglycemia, metabolic acidosis, hyperlipidemia, hypertension, nephrotoxicity, tremors, seizures, gingival hyperplasia, hypertrichosis
Sirolimus	Gastrointestinal side effects (nausea, diarrhea, stomach cramps), hyperlipidemia, proteinuria, impaired wound healing, mouth ulcers, myelosuppression, elevated transaminases, pneumonitis, headaches, acne, leg cramps, hypertension
Azathioprine	Myelosuppression, gastrointestinal side effects, elevated transaminases, rash
Prednisone	Hypertension, hyperglycemia, gastrointestinal side effects, weight gain hirsutism, edema, irritability, insomnia, acne, osteoporosis, growth suppression, poor wound healing, adrenal suppression

Given the side effects of corticosteroid use, not using them for chronic therapy would be preferable. Since the 1980s, single-center series have reported low rejection rates and comparable survival outcomes to registry data using steroid avoidance maintenance regimens [44–46]. Each of these reports, however, had different immunosuppression protocols – some varied over time within the same center and used echocardiography as the primary surveillance tool for detection of rejection. Moderate cellular rejection by endomyocardial biopsy is not necessarily associated with echocardiographic changes and therefore may underestimate cellular rejection [47].

More recently, Singh et al. reported on 55 consecutive patients from 2 centers who received the same immunosuppression protocol consisting of induction with thymoglobulin and a maintenance regimen of tacrolimus and MMF. Rejection surveillance used endomyocardial biopsy at frequent intervals during the first year posttransplant. An 87% freedom from rejection at 1 year was reported, which at the time was lower than that reported in the International Society for Heart and Lung Transplantation (ISHLT) registry. There were 15 patients considered not eligible for the protocol at the time of transplant due to high risk of antibody-mediated rejection. Excluding these patients may have lowered the incidence of early rejection in this cohort. This report was the first dual center study in pediatric heart transplantation to have a standardize immunosuppression protocol and rejection surveillance. Auerbach et al. (2014), using the Organ Procurement and Transplantation Network (OPTN) database and the Pediatric Heart Transplant Society (PHTS) database, used propensity matching to mimic randomization and were able to show no difference in graft survival between steroid-free patients and those on maintenance steroids at 1 year [48]. As is frequently the case with large registry databases, the comorbidities of steroid use, such as hypertension and diabetes, were not analyzed due to incomplete data sets. Additionally, baseline immunosuppression was not able to be analyzed in either study.

Sirolimus and everolimus are classes of drug that inhibit the mechanistic target of rapamycin (mTOR). mTOR regulates cellular metabolism, growth, and proliferation. Their use in pediatrics remains very low, with less than 2% of patients on one of these drugs at the time of transplant discharge [2]. There is evidence in the pediatric heart literature that conversion from a calcineurin inhibitor to an mTOR inhibitor as primary immunosuppression or its use with a lower dose of calcineurin inhibitor can improve renal function [49–52]. However, the adverse effects may make its use challenging. Chinnock et al. reported hyperlipidemia in 50% of patients, anemia and neutropenia in 40%, and aphthous ulcers in 15%. Asante-Korang et al. reported a significant increase in cholesterol and triglycerides with mTOR use, and leucopenia and aphthous ulcers in 32% of patients. It is thought that mTOR inhibitors may reduce the development of graft vasculopathy due to its anti-proliferating effects, though this has yet to be clearly demonstrated in pediatric heart transplant. A double-blind study of 634 de novo adult heart transplant recipients randomized to either high everolimus, low-dose everolimus, or azathioprine showed a lower incidence of graft vasculopathy at 6 months by intracoronary ultrasound and a lower rate of CMV infection in both everolimus groups compared to azathioprine [53]. A similar randomized, open-label trial using sirolimus in de novo adult heart transplant patients showed a reduction in acute rejection episodes and graft vasculopathy at 2 years [54]. In contrast, in a recent study using the Pediatric Heart Transplant Society database, no difference was found in time to rejection, hospitalization for infection, renal insufficiency, graft vasculopathy, or survival between patients on sirolimus at 1 year posttransplant and propensity-matched controls [2]. A similar study looking at early initiation of mTOR inhibitors did not show a reduction in graft vasculopathy or survival benefit, but patients treated with mTOR inhibitors had a higher rate of rejection in the first year [42].

The multiple single-center protocols for induction and maintenance immunosuppression make it difficult to make comparisons and recommendations about the ideal immunosuppressive regimen. Expansion of the evidence base relating to the efficacy and safety of these drugs in pediatric heart transplant recipients is necessary and imminent. The TEAMMATE Trial (Tacrolimus/Everolimus against Tacrolimus/MMF) recently funded by the Department of Defense is the first randomized, multicenter trial in pediatric heart transplant to compare the efficacy and safety of two drug regimens in preventing major adverse events from 6 to 36 months after transplant (clinicaltrials.gov NCT03386539). Additionally, the prospective, observational, multicenter Clinical Trials in Organ Transplantation in Children, alloantibodies in children, funded by the National Institute of Allergy and Infectious Diseases (NIAID) will give the pediatric heart transplant community a unique opportunity to look at a

cohort of pediatric heart transplant recipients treated with the same immunosuppression protocol [55]. Enrolled patients were started on a steroid-sparing protocol including 5-day thymoglobulin induction followed by maintenance therapy with tacrolimus and MMF. Target levels of tacrolimus based on time from transplant were suggested in addition to suggested guidelines for treating sensitized patients perioperatively [55].

Retransplantation

Pediatric retransplantation accounts for 5% of total pediatric transplants [56]. The lack of uniformity in patient selection, comorbidities, and length of follow-up, along with small numbers in single-center series, make it difficult to distinguish appropriate candidates from those that would do poorly after a second transplant. There have been several studies looking at large registries to assess outcome after retransplantation and to identify risk factors for poor outcome, the most recent of which uses data from the ISHLT registry [57–59]. One-year survival after retransplantation was similar to primary transplant, but long-term survival was worse. Survival after primary transplant was 84%, 72%, and 60% at 1, 5, and 10 years and in the retransplant group 81%, 63%, and 46%, respectively. The median survival in primary transplant recipients was 15 years compared to 8.7 years for retransplanted children [57].

Graft vasculopathy is the most common indication for retransplantation, accounting for more than 50% of cases [57]. It has better survival than those retransplanted for other reasons (Fig. 6.4). Survival after retransplant nears that of primary transplants but only if retransplanted longer than

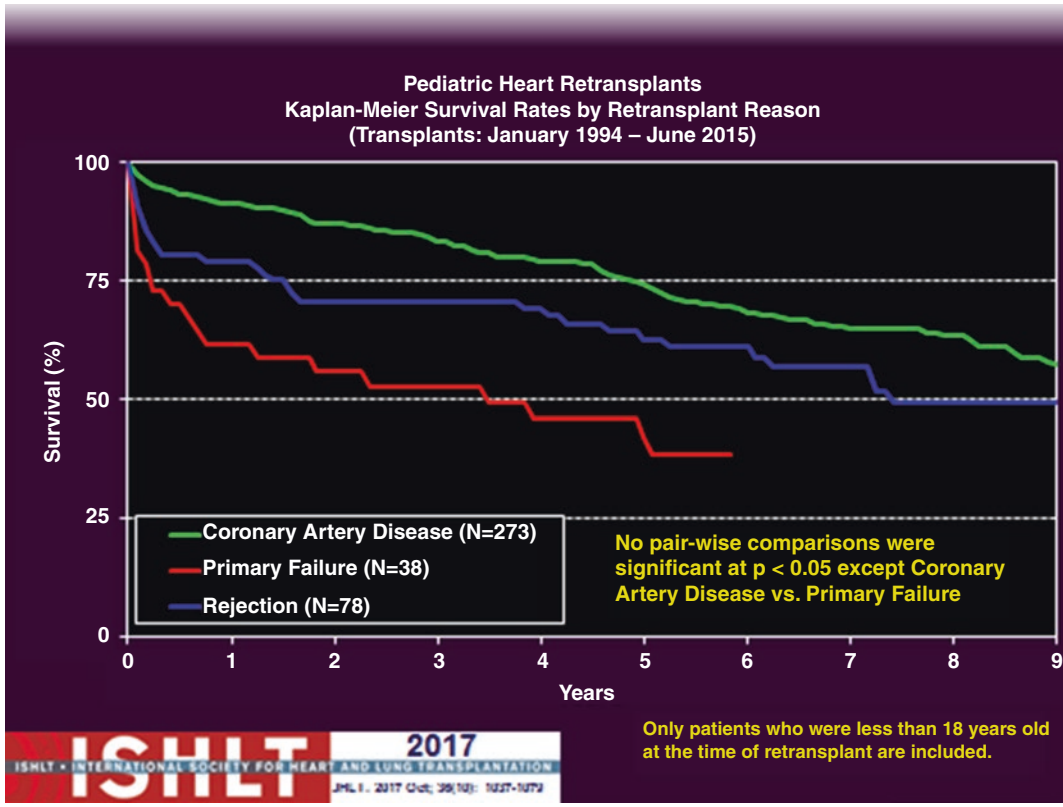


Fig. 6.4 Kaplan-Meier survival rates in pediatric heart retransplant by reason. Since many patients are still alive and some patients have been lost to follow-up, the survival rates are estimates rather than exact rates because the time of death is not known for all patients

5 years after the original transplant. Patients retransplanted less than 1 year after the initial transplant, presumably for graft failure, have the worst survival (Fig. 6.5). Multiple risk factors for poor outcome reflecting disease acuity while waiting for retransplant have been reported. They include being in the ICU, need for intubation, dialysis or cardiac operation prior to retransplant, or developing an infection prior to retransplant [57–59].

In addition to inferior survival in children who receive second transplants, there is also more morbidity associated with retransplantation. An increased rate of late rejection, graft vasculopathy, and renal failure has been reported [57]. Given these findings and the known shortage of organs and waitlist mortality in patients awaiting primary transplant, controversy will remain regarding the role of retransplantation. Transplant programs have a responsibility to their patients and need to be responsible stewards of donor organs. A careful assessment of why the first transplant failed, particularly if early after transplant, is necessary to maximize the potential for a successful second transplant and appropriate use of donor organs. Being able to risk stratify candidates who would derive the most benefit from retransplantation is imperative.

Rejection Surveillance

Rejection is a major cause of morbidity and mortality after heart transplant. Fortunately, there has been a decrease in the percentage of patients being treated for rejection early after transplant

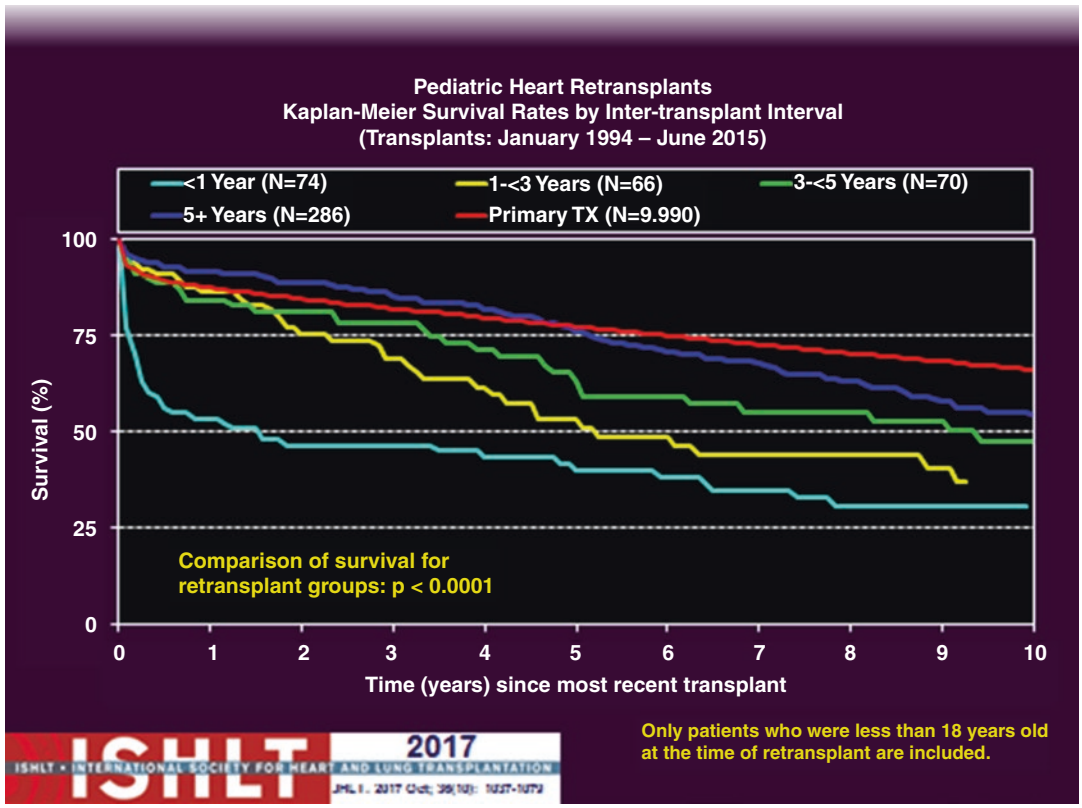


Fig. 6.5 Kaplan-Meier survival rates by inter-transplant intervals. Since many patients are still alive and some patients have been lost to follow-up, the survival rates are estimates rather than exact rates because the time of death is not known for all patients. A significant p-value means that at least one of the groups is different than the others, but it doesn't identify which group it is

in all age groups and genders [2]. Endomyocardial biopsy (EMB) is widely utilized as a surveillance method to detect asymptomatic rejection. There has been debate over the decades on the risk and benefit of endomyocardial biopsy compared to noninvasive imaging modalities to detect rejection. Endomyocardial biopsy is an invasive procedure with a complication rate in children reported from 1.1% to 4.7% [60, 61]. Infants less than 6 months and 8 kgs make up the highest-risk group for complications [61]. Centers vary in the frequency of surveillance EMB during the first year. Centers that historically have transplanted many infants have relied on noninvasive imaging, in particular echocardiography. Whether there is a difference in patient outcomes based on rejection surveillance technique and the optimal frequency of EMB is still unknown. As discussed in earlier sections, practice variation is great in pediatric heart transplant, making it challenging to answer these questions [62–64]. The Pediatric Heart Transplant Society, a consortium of 55 centers that have transplanted 6491 patients listed less than 18 years of age, has started the process of trying to answer some of these questions (http://www.uab.edu/medicine/phts/). The first step is identifying what are the practice variations in the various centers. Building consensus and drafting protocols will then lead to multicenter trials that can study rejection surveillance and the impact on outcomes in a uniform, scientific manner. The pediatric heart transplant community already has momentum in designing trials as in the CTOTC and TEAMMATE Trial discussed in previous sections; the PHTS is another example. These multicenter collaborative efforts will allow the pediatric heart transplant community to answer questions that have caused contemporary controversy.

Key Points

- Heart transplantation in children is the procedure of choice for children with end-stage heart disease.
- The indication and timing of VAD implantation depends on several factors including patient size, device availability, blood type, expected transplant wait time, etiology of heart failure, and overall condition of the patient.
- Anticoagulation remains a challenge in children on mechanical assist devices, particularly in infants and young children.
- Heart transplant survival has improved over the eras as a result of improved patient selection, ICU care, and choice of immunosuppressive drugs.

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