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Pitfalls and Future Directions of Contemporary Pediatric Valve Surgery: the Case for Living Valve Substitutes

Stephanie N. Nguyen[1] · Alice V. Vinogradsky[1] · Giovanni Ferrari[2] · Megan Sykes[3] · Emile A. Bacha[1] · Marc E. Richmond[4] · Andrew B. Goldstone[1]

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Abstract

Purpose of Review Infants and young children with congenital heart disease and valvular lesions may require valve replacement when a durable repair is unlikely. The fundamental problem with currently available valve substitutes in all positions is the lack of somatic growth potential. Young patients are therefore committed to multiple reoperations for successively larger valve replacements by the time they reach adulthood.

Recent Findings An emerging solution to this issue is allogeneic valve transplantation whereby the implanted valve is harvested from the heart of a deceased donor. The major advantage of this approach is the use of living tissue which grows adaptively with the child, thereby minimizing the number and additive risk of subsequent reoperations for valve exchange but incurring the risks of immunosuppression.

Summary Here, we review the advantages and disadvantages of currently available valve replacement options for each of the four valves. We also discuss the potential role and future directions for allogeneic valve transplantation in pediatric valve surgery.

Keywords Allogeneic Valve Transplant · Congenital Heart Disease · Partial Heart Transplant · Valve Disease · Valve Replacement · Transplantation

Introduction

Congenital heart disease is the leading cause of newborn death due to congenital anomalies in the USA [1]. Of those surviving the newborn period, approximately 25% require surgery within the first year of life [2, 3], often for valvular malformations and outflow tract lesions. Valves and valved conduits from bioprosthetic and synthetic materials are traditionally used when repair is not feasible, though no ideal substitute exists. Besides degenerative, thromboembolic, and bleeding complications, the primary disadvantage is lack of growth potential, necessitating serial reoperations to exchange nonviable prostheses for larger sizes [4]. This causes considerable morbidity and mortality, with significant psychosocial impacts on children and families.

Allogeneic valve transplantation is an emerging therapy that involves the replacement of irreparable native valves with fresh, living allografts from a size-matched donor heart. Since valves are not cryopreserved or fixed, they can grow with the child. Despite the need for systemic immunosuppression to preserve allograft viability [5•], a handful of allogeneic valve transplants have been performed to date [6, 7•]. This review summarizes pediatric valve replacement options and comments on the history and potential of allogeneic valve transplantation to deliver a valve that will grow with the patient. Historical and contemporary valve replacement options are summarized in Table 1.

✉ Andrew B. Goldstone
abg2191@cumc.columbia.edu

1 Section of Pediatric and Congenital Cardiac Surgery, NewYork Presbyterian-Morgan Stanley Children's Hospital, Columbia University Irving Medical Center, 3959 Broadway, Babies North, Suite 276, New York, NY 10032, USA

2 Department of Surgery, Department of Biomedical Engineering, Columbia University Irving Medical Center, New York, NY, USA

3 Columbia Center for Translational Immunology, Department of Medicine, Department of Microbiology and Immunology, Columbia University Irving Medical Center, New York, NY, USA

4 Division of Pediatric Cardiology, Columbia University Irving Medical Center, NewYork Presbyterian-Morgan Stanley Children's Hospital, New York, NY, USA

Aortic Valve Replacement (AVR)

Congenital aortic stenosis is present in approximately 5% of children with congenital heart disease [8] and often associated with a bicuspid valve and left ventricular outflow tract obstruction. While repairs are increasingly being performed with acceptable results [9–11], the optimal replacement option remains controversial. Contemporary AVR literature is summarized in Supplementary Table 1.

Ross Procedure

The Ross operation is an attractive option for children and young adults. The diseased valve is replaced with a pulmonary autograft and the right ventricular outflow tract (RVOT) is reconstructed using a cryopreserved or decellularized homograft. Advantages of the pediatric Ross operation include an excellent hemodynamic profile, avoidance of anticoagulation, and growth potential of the pulmonary autograft, though not the homograft [12, 13].

While technically complex, the Ross procedure is safe in children and adolescents, with operative mortality rates of approximately 1% [14•, 15•]. Several groups have also demonstrated excellent long-term survival and freedom from autograft reintervention in older children [16–28]. In a meta-analysis by Moroi and colleagues, late mortality was 0.04–1.83% per year, with annual reoperation rates for autograft failure of 0.37–2.81%. In neonates and infants, however, mortality and reintervention rates are much higher [15•]; a recent analysis of the Ross procedure using the Society of Thoracic Surgeons Congenital Heart Surgery database revealed an operative mortality of 1.5% and 0.8% in children and adolescents, respectively, compared to 24.1% and 11.2% in neonates and infants [14•]. Long-term outcomes also differ—Donald and colleagues demonstrated a 10-year survival of 78.9% in neonates and infants and 96.2% in children older than 1 year. Overall, 10-year freedom from autograft reoperation was 86%, with age younger than 1 year at operation being a risk factor [16].

The major shortcoming of the pediatric Ross operation is the need for reintervention on either outflow tract. Pathologic autograft dilation may occur at the level of the annulus, sinuses, or sinotubular junction, possibly from failure of the pulmonary autograft to adapt to higher systemic pressures [26, 28, 29]. Despite technical modifications to mitigate this risk [30, 31], these may inhibit somatic growth and

Table 1 Classification of historical and currently available valve substitutes and their advantages/disadvantages

Valve substitute	Advantages	Disadvantages
Mechanical	• Durability	• Lacks growth potential • Long-term anticoagulation • Size limitation — smallest valve (16 mm) too big for neonate/infant
Bioprosthetic/biologic		
Xenograft	• Excellent hemodynamic profile • No anticoagulation required • Limitless supply	• Nonviable — lacks growth potential • Low durability due to structural degeneration • Likely requires multiple reoperations when implanted in young patients • Increased risk of endocarditis
Homograft	• Excellent hemodynamic profile • No anticoagulation required • Easy handling	• Nonviable — lacks growth potential • Low durability due to structural degeneration • Likely requires multiple reoperations when implanted in young patients • Limited supply, especially in smaller sizes
Pulmonary autograft (Ross procedure)	• Living tissue with growth potential • Excellent hemodynamic profile • No anticoagulation required • Low risk of endocarditis	• Technically demanding operation • Converts single valve disease into double valve disease • Likely requires reoperation for homograft deterioration and/or autograft dilation
Fresh, wet-stored/homovital valves	• Contains some viable cells at the time of harvest • Excellent hemodynamic profile • No anticoagulation required • Low risk of endocarditis	• Limited availability (brain-dead donors or explanted native heart of transplant recipients) • Essentially nonviable shortly after implant without immunosuppression
Allogeneic valve transplant	• Living tissue (minimal ischemic time) with growth potential • Excellent hemodynamics • No anticoagulation required	• Presumably requires immunosuppression to maintain cell viability and growth potential • Limited donor pool • Lack of supporting preclinical data

are therefore not feasible in infants and young children. Reintervention on the right ventricle to pulmonary artery homograft is also common. Nelson and colleagues reported an overall 15-year freedom from homograft reintervention of 53%; younger age was significantly associated with homograft reintervention, with a 15-year freedom from reintervention of only 19% in neonates and infants [19]. As such, many argue that the Ross operation converts single valve disease into double valve surveillance. Nonetheless, the Ross operation is our preferred approach for AVRs in children and young adults given excellent survival, hemodynamic profile, and quality of life, with few valve-related adverse events [32•].

Mechanical Aortic Valve Replacement

Mechanical aortic valves are reserved for older children who are not Ross candidates due to connective tissue disorders or abnormal (or absent) pulmonary valves [33]. In the largest pediatric series, Myers and colleagues reported 5.5% operative mortality and 82% 10-year survival. Ten-year freedom from reoperation was 78%, with the most common reintervention reasons being pannus ingrowth and valve thrombosis and risk factors being younger age and implantation of the smallest prosthesis (16 mm) [34]. In a contemporary meta-analysis, the annual pooled mechanical AVR reoperation rate was 1.0% [35].

Though a reliable option for select patients [34, 36], a disadvantage of mechanical prostheses is the thromboembolism risk, necessitating lifelong anticoagulation. This can be challenging in children due to activity restraints, medication compliance, and use of anticoagulation in women of child-bearing age. In a recent meta-analysis, pooled annual rates of thromboembolism and major bleeding were 0.76% and 0.39%, respectively [35]. Furthermore, a root enlargement may be required to accommodate even the smallest mechanical prosthesis in neonates or infants. Finally, despite excellent durability, reoperation following mechanical AVR in children is still common—ranging from 55 to 90% at 15 years [12, 36–38]—with the main indications being patient-prosthesis mismatch, along with pannus formation causing subvalvar obstruction and endocarditis.

Bioprosthetic Aortic Valve Replacement

Tissue prostheses are commonly used in adults and allow for avoidance of chronic anticoagulation, though applications are limited in pediatrics. Prostheses are unavailable in sizes smaller than 19 mm and longevity is decreased in younger patients, in whom structural valve degeneration is typically accelerated [39–43]. Indeed, valve deterioration is 6–9 times more rapid in young adults compared to older patients, with an incidence of 30–50% at 10–20 years [44]. Saleeb and colleagues published a series of 73 pediatric patients (median age 18.8 years [range, 3.8–29.2]) who received a bioprosthetic AVR over a 15-year period. The authors noted significantly accelerated degeneration of the Mitroflow valve (Sorin Group Italia, Vercelli, Italy) compared to other tissue valves, with freedom from valve failure (explant or death) of only 20% versus 87.6% at 4 years. All explanted Mitroflows had heavy leaflet calcification and immobilization [45]. Finally, children receiving a bioprosthetic AVR will likely require multiple reoperations for patient-prosthesis mismatch due to fixed valve size.

Homograft Aortic Valve Replacement

Homografts are obtained from deceased donors and cryopreserved for prolonged storage. Though associated with excellent early hemodynamic profiles, homografts can exhibit rapid structural degeneration and failure. In pediatric patients undergoing homograft AVR, Fukushima and colleagues observed a 10-year freedom from structural valve degeneration of only 55%. Younger age was associated with structural failure [46], presumably due to higher cardiac output and a more active immune response in children [47–49]. Other groups reported similar rates of reintervention for homograft structural degeneration in young patients [18, 36, 48–52]. Wider use of aortic homografts is also restricted by the limited number of grafts in small sizes; homografts are thus generally utilized when the Ross is not feasible or when a mechanical AVR is not advisable [18].

Aortic Valve Neocuspidization (Ozaki Procedure)

The Ozaki procedure involves the replacement of diseased aortic valve cusps with tailored neocusps of autologous pericardium or synthetic patch material. Ozaki and colleagues first published on this technique in adults, with 10-year survival and freedom from reoperation of 86% and 95%, respectively [53]. The procedure has since been performed with acceptable short-term outcomes in children: Baird and colleagues reported a 2-year freedom from moderate or greater aortic regurgitation or stenosis of 88% and freedom from reoperation of 91% at 1.5 years in a cohort with a median age of 12.4 years [54].

Despite promising short- to mid-term outcomes in older children [54, 55], the long-term durability and eventual mode of failure remain unknown. Importantly, synthetic patch material clearly reduces durability [56], and observations of reduced leaflet motion have led to nearly half of Ozaki neocuspidization recipients requiring coumadin. Applications in younger children may thus be limited by this poor durability and lack of growth potential of synthetic material.

Pulmonary Valve Replacement (PVR)

The pulmonary valve is often replaced in congenital patients, with an increasing need for PVR as more survive to adulthood. Contemporary PVR literature is summarized in Supplementary Table 2.

Bioprosthetic Pulmonary Valve Replacement

Few have evaluated the optimal bioprosthetic PVR in pediatric patients [57–62], with modern understandings often extrapolated from the adult AVR experience. We analyzed the Inspiris Resilia valve (Edwards Lifsciences, Irvine, CA)—a prosthesis commonly used for AVR in adults—in the pulmonic position in children and young adults with congenital heart disease. Among propensity-matched patients, 2-year freedom from valve failure was lower in the Inspiris group compared to those who did not receive an Inspiris valve (53.5% vs. 78.5%, $p=0.03$), with prosthetic regurgitation being the main mechanism of failure. Inspiris durability was also poorer when implanted in the native RVOT compared to as a conduit, with 18-month freedom from valve failure of 59.0% vs. 85.9% ($p=0.03$) [57]. In another large, single-center study, Nomoto and colleagues showed good short-term outcomes among all studied bioprosthetic PVR options, though younger patients had almost fivefold greater risk of reintervention than adults (independent of valve type). This risk decreased by 10% for each increasing year of age at surgery [58]. Calderone and colleagues reported a 5-year freedom from valve replacement of 81%, with younger age associated with early prosthetic failure [59]. While the current bioprosthetic PVR strategy is oversizing to facilitate future valve-in-valve procedures, this is associated with structural valve deterioration and should be performed with caution [60].

Mechanical Pulmonary Valve Replacement

Mechanical valves are rarely used in the pulmonary position due to thrombosis concerns in the low pressure, right-sided system. Still, the risk profile is relatively favorable [61–66]. A multicenter retrospective analysis of 364 patients reported a freedom from valve thrombosis of 91% and 86% at 5 and 10 years, respectively. The annual incidence of valve thrombosis was 1.7%. Major bleeding complications were not reported. Durability was excellent, with 97% and 91% freedom from reintervention at 5 and 10 years, respectively [61]. As PVR patients have often had multiple prior sternotomies, a mechanical prosthesis may thus be reasonable to limit further interventions, though requires systemic anticoagulation.

Transcatheter Pulmonary Valve Replacement (TPVR)

Transcatheter pulmonary valve implantation is used to treat failing RVOT conduits or bioprosthetic pulmonary valves and is standard of care provided anatomy is favorable [67–71]. Available balloon-expandable valves include the Melody valve (Medtronic, Minneapolis, MN) made from stented bovine jugular vein and SAPIEN transcatheter bovine pericardial valve (Edwards Lifesciences, Irvine, CA). The Melody Investigational Device Exemption trial demonstrated an estimated 10-year survival of 90%, along with 79% freedom from RVOT reoperation and 60% freedom from any valve reintervention. Ten-year freedom from valve dysfunction was 53% and significantly lower in children than adults [68]. While this trial affirmed the role of TPVR technologies in the lifetime management of patients with repaired congenital heart disease and a dysfunctional RVOT conduit or pulmonary valve prosthesis, young patients inevitably outgrow the implant. Additionally, the risk of endocarditis appears to be higher with these devices.

Right Ventricle-to-Pulmonary Artery Conduits

Reconstruction of right ventricle-to-pulmonary artery (RV-PA) continuity is integral to congenital cardiac surgery repairs. Factors influencing the choice of conduit include original pathology, age, and availability. All conduits, however, do not grow, making serial reoperations unavoidable [72]. Contemporary RV-PA conduit literature is summarized in Supplementary Table 2.

Homografts

Pulmonary and aortic homografts have favorable handling properties, are available in sizes small enough for infants, and have low infection risk. Disadvantages, however, are lack of growth potential, risk of structural degeneration and calcification, high cost, short shelf-life (~2 years), and limited availability in sizes small enough for neonates or large enough for younger children. Furthermore, some patients may develop human leukocyte antibodies after homograft implantation and this sensitization may increase the risk for antibody-mediated rejection and graft dysfunction should the patient require a future heart transplant.

In regard to homograft durability, freedom from reintervention ranges widely—30 to over 80% at 10 years [73–80]—with smaller conduit size, younger age at operation, and a non-Ross operation being risk factors for conduit failure [75, 81, 82]. Several series have also demonstrated superior durability of pulmonary over

aortic homografts [73, 81, 82]. Lewis and colleagues reported a series of 455 consecutive pediatric patients (mean age 6.4 ± 5.8 years) who underwent RV-PA conduit reconstruction with either a pulmonary homograft, aortic homograft, or bovine jugular vein graft and demonstrated a 10- and 28-year freedom from conduit replacement of 79.6% and 66.0%, respectively, for pulmonary homografts, compared to 49.8% and 23.0%, at 10 and 30 years, respectively, for aortic homografts [73]. Pseudoaneurysms and conduit dilation, however, are more common with pulmonary homografts [83].

Xenografts

Xenografts of bovine or porcine origin may be stented or non-stented. Advantages include abundant supply, availability in small sizes, favorable handling characteristics, and low cost compared to homografts [84]. One of the most used, the Contegra xenograft (Medtronic, Minneapolis, MN), is made from valved bovine jugular vein and small enough for infant RVOT reconstruction. Durability is at least comparable to pulmonary homografts [85–89], though younger age at implantation is a risk factor for reintervention and distal conduit stenosis [90]. Importantly, the Contegra homograft is associated with increased risk of endocarditis compared to other biological conduits [86].

Synthetic Valved Conduits

Composite valved conduits made of synthetic tube grafts with bioprosthetic or mechanical valves are available commercially or can be manually constructed [91]. Commercially available conduits include the Hancock (Medtronic, Minneapolis, MN), consisting of a porcine valve within a Dacron tube [92]. Advantages include prolonged shelf-life, widespread availability, and a rigid pericardial valve annulus resistant to sternal compression. Size limitations, however, limit use in neonates and small infants.

Mitral Valve Replacement (MVR)

Rheumatic heart disease, endocarditis, mitral stenosis, and failed atrioventricular septal defect repair are the most common indications for MVR in pediatric patients. Unfortunately, MVR carries the highest operative and long-term mortality risk of all pediatric valve replacements [93–95]. Contemporary MVR literature is summarized in Supplementary Table 3.

Mechanical and Bioprosthetic MVR

Surgical MVR operative mortality in infants and young children is 10 to 36% [94–97]. In a multi-institutional study of 139 patients under 5 years old, Calderone and colleagues reported 74% 10-year survival. Most deaths occurred shortly after initial MVR and 5-year freedom from reoperation was 81% among survivors. An increased ratio of valve size to patient weight was an age-adjusted predictor of death [94]. This is notable as valves are often oversized and implanted in a supra-annular position in infants and small children, leading to leaflet entrapment, left ventricular outflow tract obstruction, and atrioventricular block [94–96]. Other studies have also found both of these techniques to be associated with increased mortality [93, 98–100].

Despite oversizing, prosthetic valves must be replaced given lack of growth potential. Choi and colleagues reported freedom from redo MVR of 76% and 44% at 5 and 10 years, respectively; time to reoperation was associated with prosthesis type, with porcine and pericardial valves at greatest risk. Prosthesis type was also associated with time to death or transplant, with porcine valves at greater risk than mechanical valves [101•]. Still, mandatory anticoagulation and size limitations remain a disadvantage of mechanical valves.

Transcatheter MVR

Given poor outcomes and size limitations, stented bovine jugular vein valves (Melody valve, Medtronic, Minneapolis, MN), originally approved for TPVR, have been implanted in the mitral position as an off-label use [102]. Valves are initially surgically implanted into a small mitral annulus and serially balloon-dilated to accommodate somatic growth [103]—this technique has been employed as a bridge to a future fixed-diameter valve replacement with acceptable short- and mid-term outcomes [104, 105]. Choi and colleagues demonstrated that stented bovine jugular vein valves may exhibit greater durability than conventional xenograft prostheses in small children. All balloon dilations performed on Melody valves were successful in resolving or significantly decreasing the transmitral gradient, with only 11.8% of patients developing mitral regurgitation [101•]. While paravalvular leaks are common, this is likely related to surgical implantation technique and device design.

Tricuspid Valve Replacement (TVR)

TVR is rarely performed in young children, most often for irreparable Ebstein's anomaly and tricuspid valve dysplasia. Reports on pediatric TVR consist of small series from single institutions, with early mortality of 9–36% [106–109]. Contemporary TVR literature is summarized in Supplementary Table 4.

Bioprosthetic and Mechanical Tricuspid Valve Replacement

Several adult studies have demonstrated acceptable tricuspid bioprosthesis durability [110–112], though few have been performed in children. Boyd and colleagues recently reported disappointing results with bioprosthetic TVR for Ebstein's anomaly: compared to cone repair, the valve replacement group had a lower freedom from reoperation at 6 years (cone: 91% vs. TVR: 68%, $p=0.02$) and worse right ventricular function at mean follow-up of 4 years [113]. In an older series, however, Kiziltan and colleagues reported favorable long-term outcomes in 158 patients with Ebstein's anomaly or an Ebsteinoid valve undergoing TVR with a porcine bioprosthesis: 15-year survival and freedom from reoperation was 92.5% and 80.6%, respectively. Of note, bioprostheses demonstrated higher freedom from reintervention than mechanical prostheses [109]. Similarly, Bartlett and colleagues saw improved survival and lower rates of pacemaker requirements in children who received bioprostheses compared to mechanical TVR. Implantation of a large valve relative to the patient's weight was a predictor of postoperative mortality, indicating that oversizing to delay replacement may impair ventricular dynamics and restrict leaflet mobility [107].

Overall, mechanical prostheses are rarely used in the tricuspid position due to valve thrombosis risk, with reported incidence of 3–18% [110, 114]. As such, anticoagulation with a higher International Normalized Ratio goal is required, significantly increasing the risk of bleeding complications.

Historical Use and Development of Viable Allograft/Homograft Valves

The initial orthotopic implantation of aortic valve allografts was reported in 1962 by Ross [115] and Barrett-Boyes [116]. Valves were collected at autopsy, minimally treated, and implanted within hours to days. Outcomes were favorable, with the New Zealand group reporting 79% survival and 13% incidence of valve failure at 6 years [117]. Over the next decades, multiple centers published their experience with fresh homograft valve replacements [118–125].

Initial procedures were performed utilizing freshly harvested valves from brain-dead donors or explanted hearts of transplant recipients. Valves were antibiotic-sterilized, stored in nutrient media at 4 °C for up to 6 weeks, and implanted at first opportunity. Such "fresh, wet-stored" homograft valves contained viable cells and were called "homovital" valves. Stanford published on 83 patients who received fresh aortic homografts between 1967 and 1971 and demonstrated a 5-, 10-, and 15-year freedom from valve failure of 83%, 62%, and 43%, respectively. Freedom from reoperation was 88%, 67%, and 45% at 5, 10, and 15 years, respectively [119]. Yacoub's group also reported their 14-year experience with 275 homovital aortic valve replacements. Freedom from degenerative valve failure was 94% at 5 years and 89% at 10 years [126]. This experience supported that fresh, wet-stored homografts were valuable valve substitutes with good performance data. Donor availability, however, limited widespread use and led to development of current preservation techniques.

In 1975, O'Brien described the cryopreservation of fresh valves using a dimethylsulfoxide controlled-rate freezing technique with storage in liquid nitrogen at − 190 °C [127]. In a series of 192 cryopreserved aortic allografts, the Brisbane group demonstrated 100% freedom from reoperation for valve degeneration at 10 years. Moreover, cryopreserved valves recovered from patients dying of non-valve-related events up to 9.5 years later demonstrated preserved donor fibroblast viability [128]. In 2001, their follow-up series demonstrated that freedom from reoperation for structural deterioration of cryopreserved valves was recipient age-dependent: at 15 years, freedom was 47% (0–20 years), 85% (21–40 years), 81% (41–60 years), and 94% (> 60 years) [129]. This reflects Yacoub's findings—fresh allograft durability was worse in younger patients, possibly due to recognition of viable cells by a more active immune system.

The degree of cell viability at the time of cryopreserved valve implantation and the rate of cell loss over time is ultimately unknown. It is also unclear whether durability is related to viable donor fibroblasts, improved matrix preservation by cryopreservation, or both. Notably, most early work did not utilize ABO or human leukocyte antigen tissue matching criteria or immunosuppression. Given the overall success with cryopreserved valves and convenience of tissue banking, cryopreservation has become the standard preservation method in modern times. Loss of viability and age-dependent structural degeneration, however, remain the main limitations of cryopreserved homografts.

Delivery of a Living Valve Substitute: Allogeneic Valve Transplantation

There is a critical need for valves with growth potential. Engineering valves capable of growth and regeneration is of great interest, though has failed to achieve clinical translation [130]. Recently, there has been renewed interest in fresh allografts with modifications to preserve viability. Termed "partial heart transplant" or "allogeneic valve transplant," size-matched donor hearts from a brain-dead donor or explanted hearts of heart transplant recipients are procured [131•]. Semilunar (and possibly atrioventricular valves) are explanted and used to replace diseased recipient valves. This may eliminate the need for anticoagulation and serial reoperations since the allograft should grow with the patient. The major drawback, however, is the presumed need for immunosuppression and its attendant risks.

To date, our group and two others have performed a handful of allogeneic valve transplants in infants with truncus

arteriosus [6, 7•]; the common truncal root was replaced by donor aortic and pulmonary roots to create two outflows. Recipients are maintained on variable immunosuppression regimens (Fig. 1A), though most are less intense than those used for traditional orthotopic heart transplant. When the child reaches adulthood, the valve may be replaced by a larger prosthesis and immunosuppression discontinued.

Immunologic Considerations of Viable Valve Allografts

Data guiding long-term management are lacking. Some believe that a reduced dose of immunosuppression may be allowable since cardiac valves are less immunogenic than whole cardiac allografts and may even be immune-privileged tissue [131•, 132•]. Mitchell and colleagues examined aortic valves from rejected transplanted hearts and found no evidence of immune injury and entirely preserved cellularity and architecture [133]. Mohri and colleagues orthotopically implanted fresh canine aortic valve allografts into pre-sensitized animals and found no evidence of immune infiltration in the transplanted leaflet at 3 months, but rather signs of re-endothelialization [134]. This concept is further supported by echocardiographic data, which show preserved semilunar valve function despite severe ventricular dysfunction in the setting of acute rejection [135•]. While the mechanism through which valves possess low immunogenicity is unknown, this may be due to the lack of valve tissue vascularity as cellular and antibody-mediated rejection typically occur at the level of the ventricular microvasculature [132•].

Others contend that valves can elicit an immune response [136–139], with immunogenicity attributed to surface antigens on valve endothelial cells that may attract cytotoxic lymphocytes and induce lymphoproliferation [136]. Hogan and colleagues demonstrated increased recipient T-cell alloreactivity toward donor lymphocytes and persistence of human leukocyte antigen antibodies in patients who received fresh aortic valve allografts [138]. Heslop and colleagues implanted fresh aortic valve allografts into the abdominal aorta of rats and found that immune injury was limited to the rim of myocardium beneath the valve—the aortic wall demonstrated mild antigenicity, but valve leaflets did not show inflammatory changes [139]. Ultimately, additional investigations to determine the extent to which immunosuppression is required to maintain a functional valve are needed.

Future Directions

Though in its infancy, allogeneic valve transplantation is a promising strategy for delivery of a living, viable valve substitute to pediatric patients with irreparable valve disease. For wider incorporation into current practice, safety and efficacy must be further evaluated. The South Carolina group recently proposed a prospective, observational study evaluating safety, feasibility, growth, and function of allogeneic valves [5•]. As these valves are not amenable to biopsy, alternative methods to detect allograft rejection are needed, as are methods to determine the appropriate amount of immunosuppression required for long-term valve function.

We propose that donor hearts declined for conventional transplantation and explanted native hearts of transplant recipients be evaluated for valve donation (Fig. 1B). Additional investigations into valvular cell fate, as well as optimal preservation methods, are also required. Prolonged storage, while maintaining viability, will allow for an extended travel radius for procurement and may have a substantial economic and environmental impact if local procurement teams could obtain and deliver the valve to the recipient hospital by commercial courier services, as is done for kidney transplants.

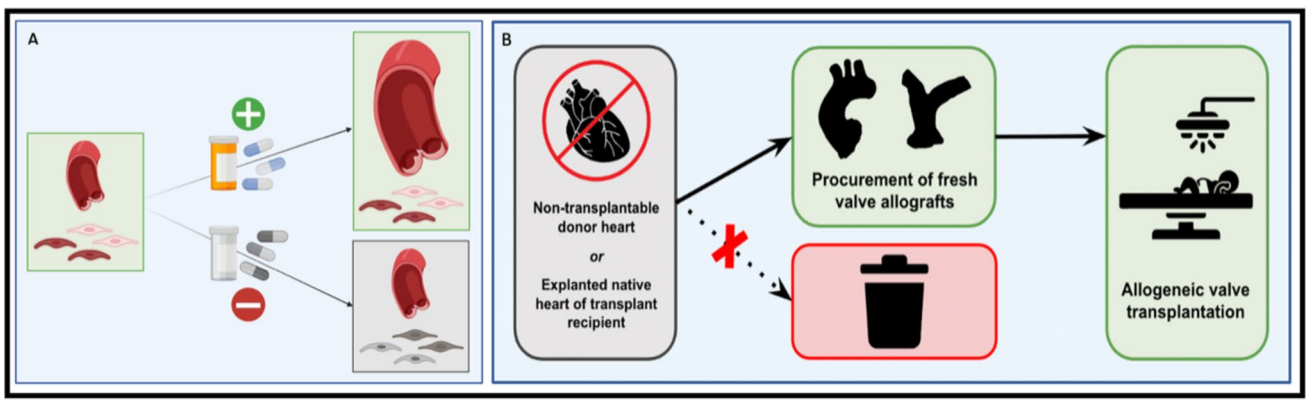

Fig. 1 Illustrative schematic demonstrating: **A** presumed role of systemic immunosuppression in preserving valve cell viability and growth potential after allogeneic valve transplant; **B** donor cardiac allografts deemed non-transplantable and explanted native hearts of transplant recipients—without valvulopathy—may be utilized as a source of fresh valve allografts for allogeneic valve transplantation

While the major drawback of allogeneic valve transplant is the presumed need for immunosuppression, methods of inducing graft tolerance under investigation include: (i) thymic co-transplantation, wherein recipient T lymphocytes are educated within the transplanted donor thymus after recipient treatment with T cell–depleting antibodies, and (ii) mixed chimerism, wherein bone marrow-derived cells from both donor and recipient coexist [140, 141]. Most success with these techniques has been in the realm of renal transplantation [142–146], though investigators recently induced donor-specific tolerance with thymic co-transplantation in cardiac allografts for up to 182 days [147]. Finally, advancing our understanding of immune principles in this domain may serve as a platform for future studies in xenogeneic valve transplantation, which could produce a nearly unlimited source of valves [140].

Conclusions

Pediatric valve disease remains a challenging problem in pediatric and congenital cardiac surgery. Currently available valve prostheses lack growth potential, and infants and young children require multiple reoperations. The theoretical growth potential, durability, and lack of anticoagulation of living valve allografts may mitigate the morbidity associated with existing valve replacement options for infants and children. While the major limitation of allogeneic valve transplant is the presumed need for immunosuppression, additional preclinical studies may better reveal the extent to which immunosuppression is required to maintain a functional valve. Still, allogeneic valve transplantation may soon shift the treatment strategy for pediatric valve disease.

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Declarations

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