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Review

Pediatric Heart Transplantation: A Progress Report

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Abstract

Following the first orthotopic heart transplant performed in 1967, pediatric heart transplantation procedures, have undergone significant advances over the last five decades. Subsequently, survival times have improved over the years, whereby those receiving an orthotopic heart transplant now survive for decades longer. A significant advancement in this area involves the management of blood type (ABO) incompatibility. Recent protocols and antibody-mediated therapies have made ABO-incompatible transplants more feasible, improving graft survival. Real-time evaluation and optimization of donor hearts have also been revolutionized by expanding donor sources through donation after circulatory death. Innovation in management and preservation techniques has demonstrated that donations after circulatory death have acceptable post-transplant outcomes. Immunosuppressive therapy has also evolved with the emergence of tacrolimus monotherapy, which is gaining attention as a potential strategy for reducing the risks associated with polypharmacy while maintaining graft function. Moreover, *ex-vivo* perfusion systems have optimized donor heart preservation by reducing cold ischemia time and improving graft quality. With advancements in systems and processes, surgical procedures for partial heart transplantation have shown promise for selected patients. Ultimately, xenotransplantation is an emerging frontier in addressing the persistent organ shortage. Thus, this manuscript presents a comprehensive review of the progress in pediatric heart transplantation over the past decade, as well as the prospects for this field of research.

Keywords: pediatric heart transplantation; donation after circulatory death; immunosuppression; *ex-vivo* perfusion system; partial heart transplant; ABO-incompatible transplant; xenotransplantation

1. Introduction

Since its inception in 1967 [1], pediatric heart transplantation has revolutionized the care of pediatric patients with end-stage heart disease worldwide. There has been substantial progress in pediatric heart transplantation over the past few decades. The progress has been outlined below in a chronological fashion.

Before the 1980s was the pre-cyclosporine era, when long-term patient and graft survival was the exception and not the rule for adult patients managed with steroids and azathioprine-based immunosuppression [2,3]. The International Society for Heart & Lung Transplantation (ISHLT) registry retrospective review showed that the 30 children who underwent pediatric heart transplantation before 1982 had a median survival of 3.5 years, with the first child who survived more than a year after transplantation in 1968 [4]. The 1980s saw the transformation of the field with the introduction of cyclosporine, which eventually led to the current approach of combined immunosuppressant agents targeting different mechanisms of the immune system to minimize both acute and chronic rejection [5,6]. Eventually, in the 1990s, allocation policies for heart transplantation were revised to prioritize infants less than 6 months of age, given high waitlist mortality along with heart transplantation transitioning to being reserved for infants unsuitable for, or with failed, surgical palliation [7,8]. The 2000s were when positive crossmatch and blood type (ABO)-incompatible heart transplantation were explored [9]. Ultimately, the 2010s saw major advances in pediatric mechanical support that extended the capability to bridge pediatric patients to heart transplantation [9]. Further, the care of pediatric heart transplant patients is complex and over the years has seen thorough multidisciplinary care, especially when it is team-based and patient-centered, playing an important role in improving the outcomes related to pediatric heart transplantation [10,11].

Significant advancements in the current decade include donor source expansion with donation after circulatory death, further advancements in immunosuppression, organ preservation innovations such as the development of *ex-vivo* perfusion systems, and emerging surgical techniques such as partial heart transplantation. The number of pediatric heart transplants has increased by 94.9% over the decade, from 25 transplants in 1987 to 494 transplants

in 2022, with the number of transplant centers increasing from 19 to 55 [12]. Along with the increase in numbers, the 1-year graft survival rate has also steadily increased, reaching an all-time high of 97.2% in 2021 [12]. This survival represents a stark improvement from early reported 1-year graft survival rates of 38.9% in 1987 and 22.8% in 1988 [12]. Challenges persist despite the advancements. Waitlist mortality remains a significant concern, with recent data showing 12-month survival rates of approximately 79.6% for listed patients [13]. The field has future unmet challenges, including further research on ABO-incompatible heart transplantation and xenotransplantation.

In this review, we will to provide an overview of significant advancements in the field and the progress made in the current decade. We will also highlight the future unmet challenges of pediatric heart transplantation.

2. Brief History of Pediatric Heart Transplantation

The field of pediatric cardiac transplantation was shaped by several pioneering surgeons, cardiologists, and teams whose work established the foundation for modern pediatric heart transplant. Among the key figures that contributed to this field is Dr. Adrian Kantrowitz who performed the world's first pediatric heart transplant in 1967, just three days after the first adult heart transplant by Dr. Christiaan Barnard [14]. The recipient died 6.5 hours after the procedure, and Dr. Kantrowitz never pursued clinical heart transplantation [14]. It would be 16 years before neonatal heart transplantation was again attempted. Further, Dr. Magdi Yacoub is renowned for pioneering pediatric heart transplantation. Dr. Yacoub performed early transplants in infants and children in the 1980s in London [14]. His work helped advance surgical techniques and postoperative management in young patients [14]. It was eventually in 1985 when Dr. Leonard Bailey performed the first successful neonatal heart transplant in 1985 on a baby with hypoplastic left heart syndrome, at Loma Linda University [14]. This case demonstrated the feasibility of heart transplantation in infants and led to broader acceptance of the procedure in neonates. In 1968, Dr. Norman Shumway, led the first successful adult heart transplant in the United States and was instrumental in advancing pediatric heart transplantation [15]. His team at Stanford performed pioneering pediatric transplants in the early 1980s [15]. In 1993, the Pediatric Heart Transplant Society (PHTS) was co-founded by Dr. James Kirklin and it became a critical registry for advancing research and outcomes in pediatric heart transplantation [16]. Dr. Robert Morrow at the University of Arkansas for Medical Sciences/Arkansas Children's Hospital was also co-founder of the PHTS, and he played a significant role in data collection and research that improved pediatric transplant practices [16]. These masterclass physicians laid the groundwork for pediatric heart transplantation.

3. Overview of Significant Advancements in the Field

3.1 Donor Source Expansion

There is an urgent need to expand the supply of hearts available for transplantation. Between 2011 and 2024, heart transplants in adults increased by 85.8% and 31.7% in children [17]. Despite this rise, 4010 Americans on the transplant list did not receive a new heart in 2019 [18]. Traditionally, donation after brain death has been the standard for heart transplants and it allows for the heart perfusion with oxygenated blood until procurement. The method prevents the warm ischemia associated with donation after circulatory death (DCD). That is why it was the standard for heart transplants; however, not including donor organs available due to circulatory death limits the number of organs available for transplantation. Given this need to expand donor heart availability, organ DCD was explored in the early 2000s [19,20]. Solid organ transplants for the past 30 years have used DCD organs, and 17% of the 36,544 transplants performed in 2020 were performed using DCD criteria [21]. This method has been implemented slowly, with no DCD heart transplants completed in 2018, but quickly expanded to 126 DCD heart transplants in 2020. Utilizing donations after brainstem death (DBD) and DCD organs can drastically expand the availability of donor's hearts, as 26% of the 15,812 donors in 2020 were from DCD [22].

Building on the success seen in the adult population, DCD began to be considered in pediatric transplants, given the higher waitlist mortality compared to other organs [23]. A single-center observational matched cohort study compared patients who received heart transplants from DCD donors with matched recipients who received transplants from DBD donors. 28 DCD heart transplants were performed, with nearly equal numbers of hearts procured through either normothermic regional perfusion or direct procurement and perfusion. Results showed that survival rates at 90 days were 92% for DCD and 96% for DBD. The study also assessed hospital length of stay, allograft function, and 1-year survival rates, which were 86% for DCD and 88% for DBD [24]. Furthermore, results from a single-institution retrospective study conducted by Cedars Sinai Medical Center published that heart transplants following circulatory death had similar short-term (6-month) postoperative outcomes compared to heart transplants following brain death (92.1% and 92.6%, respectively) [25]. In addition, a multicenter, randomized controlled trial of DCD heart donation utilizing direct procurement and MP (Transmedics Organ Care System, Transmedics Andover, MA, USA) in the United States subsequently demonstrated that DCD had no significant difference from DBD procurement in short-term outcomes [26].

Studies continue to show that DCD organs are a viable option for heart transplantation and should be utilized, especially with the widening gap between the supply of hearts

available for transplantation and the demand for transplants needed.

3.2 Immunosuppression Advancement

This first pediatric heart transplant was performed on an 18-month-old with Ebstein anomaly in 1968 by Dr. Kantrowitz [27]. This transplant and many others over the next few years made it evident that many of the deaths were related to transplant rejection. By the start of 1980, calcineurin inhibitors began to make long-term heart transplant survival a reality [28]. One of the original calcineurin inhibitors was cyclosporin A. This drug binds to cyclophilin in the cytoplasm of T-cells, subsequently inhibiting calcineurin. This inhibition leads to decreased T-cell activation and reduced cytokine gene production [29]. However, tacrolimus, another calcineurin inhibitor, has replaced cyclosporin A in most transplant protocols. Tacrolimus works by binding to FK-binding protein-12 in T-cells [30]. Tacrolimus does not come without its drawbacks. Tacrolimus has pharmacokinetics that can vary widely from patient to patient. It has a half-life ranging from 4 to 41 hours [31], which can make it difficult to achieve and maintain therapeutic trough levels and can contribute to poor patient outcomes such as an increased risk of toxicity [32]. Tacrolimus has also been linked to nephrotoxicity, hypertension, new-onset diabetes mellitus, and gastrointestinal toxicity [33]. However, tacrolimus has been a vital drug in providing immune suppression in heart transplants to avoid rejection. It has shown reduced acute rejection rates and increased time free from rejection when compared to previous standard-of-care drugs like cyclosporine A [34,35].

Different immunosuppressive strategies are essential for successful pediatric heart transplantation, each bringing unique benefits and drawbacks. Modern approaches, often combining tacrolimus, mycophenolate mofetil, and induction therapy, are associated with fewer episodes of early rejection than older cyclosporine-based triple therapy, but they may raise the likelihood of anemia and neutropenia [36]. Induction therapy further decreases the risk of acute rejection episodes, although it does not enhance long-term survival and may heighten susceptibility to infections [23,36]. Protocols that avoid or withdraw steroids help prevent complications such as growth delays and metabolic problems, without significantly compromising graft survival [23]. The use of mammalian target of rapamycin (mTOR) inhibitors (sirolimus, everolimus) can help lessen the toxic effects of calcineurin inhibitors and may decrease the risk of chronic graft vasculopathy, but their application in children is less common and can result in specific side effects [23].

Moving forward, many different regimens are used in the immunosuppression treatment for pediatric heart transplants. Immunosuppression in pediatric heart transplant recipients typically begins with induction therapy, using cytolytic agents. This therapy is initiated just before the transplant, followed by a maintenance immunosuppression regimen. Maintenance therapy may involve various medications, including corticosteroids, calcineurin inhibitors, antiproliferative agents, and inhibitors of the target of rapamycin [30]. As improvements in the understanding of immunology and immunosuppression advance and given the complexity of children with developing immune systems, more patient-specific regimens will be ideal for outcomes [37]. Some immunosuppressive regimens have excluded the use of steroids to prevent adverse side effects. A study by Hartje-Dunn *et al.* [38] looked at medium-term outcomes in 181 pediatric heart transplant recipients with steroid avoidance and tacrolimus-based immunosuppression regimens. The study also showed a graft survival rate of 94% at one year and 87% at five years in patients with low risk for antibody-mediated rejection [38]. This data suggests that tacrolimus monotherapy could be a viable option to prevent graft rejection in transplants and avoid the adverse side effects of steroids.

3.3 Organ Preservation Innovations

Perfusion of donor hearts via *ex-vivo* perfusion systems enables resuscitation, preservation, and assessment of donor hearts in a near-physiologic, normothermic, and beating state [39]. These *ex-vivo* perfusion systems enable beating heart transplants. Conventional DCD heart transplantation involves traditional static cold storage with two cardioplegic arrests, two warm ischemic periods, and two cold ischemic periods [40,41]. The use of an *ex-vivo* perfusion system enables the explanted heart from the donor to have uninterrupted coronary perfusion as it keeps the heart beating through implantation [40,41].

The perfusion platform for *ex-vivo* hearts approved by the U.S. Food and Drug Administration (FDA) for clinical use is TransMedics Organ Care System (OCS; TransMedics, Inc., Andover, MA, USA) [42]. TransMedics OCS circulates normothermic oxygenated perfusate directed to the aorta and the coronary arteries [39]. Deoxygenated blood returns from the coronary circulation to the right atrium, passes through the tricuspid valve to the right ventricle, and is ejected through the pulmonary artery back to the reservoir for recirculation [39]. TransMedics OCS also monitors vital hemodynamics such as aortic pressure and coronary flow, correcting electrolyte imbalances and acid-base disturbances as needed [39].

The use of this technology allows reduced cold ischemia times of hearts procured after brain or circulatory death since the heart remains in a normothermic state. It also enables the evaluation of extended-criteria donor (ECD) hearts along with the extension of safe *ex-vivo* time and expansion of the donor pool [39]. It also extends the *ex-vivo* safety time window for both DBD and DCD hearts, enabling increased transportation distances and further reducing geographic barriers. Specifically for DCD hearts,

it enables optimal maintenance and assessment of the heart post-circulatory cessation [43].

The EXPAND trial was the first prospective, single-arm, multi-center pivotal study in the United States to evaluate clinical outcomes using the OCS for extended-criteria DBD donor hearts [44]. 150 (87%) out of 173 ECD DBD hearts were transplanted. The 30-day survival was 97%, and the incidence of severe primary graft dysfunction was 6.7%. The mean number of heart graft–related serious adverse events within 30 days was 0.17 (95% CI: 0.11–0.23). Patient survival was 93%, 89%, and 86% at 6, 12, and 24 months, respectively, comparable with concurrent nonrandomized control subjects. A meta-analysis of 12 studies with a total of 741 donor hearts, with 260 using the OCS, demonstrated the safety and efficacy of the OCS in both DBD and DCD donations [45]. The early and late survival outcomes were similar between the OCS and traditional static cold storage groups [45]. Krishnan *et al*. [41] further published their experience at Stanford of 10 patients between 2022 and 2023 who underwent beating heart transplantation and found that all the patients survived, none had initiation of extracorporeal membrane oxygenation postoperatively, and no other mechanical circulatory support (including intra-aortic balloon pump) was initiated postoperatively.

Despite the benefits of an *ex-vivo* organ perfusion system such as TransMedics OCS for heart transplantation, several challenges prevent its widespread adoption. Some concerns include needing a larger, more specialized organ procurement team equipped with extensive personnel, equipment, and technical support. Since OCS requires constant evaluation of the donor's heart by checking lab samples and adjusting flow rates [42,46]. There is also a higher cost associated with such a system. The cost of heart transplantation can currently exceed 1.5 million dollars, and the OCS would increase costs upwards of $60,000 to $80,000 [46]. Recent studies have also questioned the effectiveness of lactate levels in predicting outcomes after OCS use [46]. In addition, there are challenges surrounding extended intensive care unit stay and postoperative circulatory support needed for some patients [47]. Appropriate perfusion poses a further challenge for widespread use of the OCS and it can be related to the high flow rate requirement [47,48].

While the OCS device is a promising tool in pediatric heart transplantation, further studies are necessary to optimize its usage and assess the long-term impact on pediatric heart transplant survival.

3.4 Emerging Surgical Techniques

The surgical technique of heart transplantation, popularized by Dr. Norman Shumway, of biatrial anastomosis [49–51] has continued to evolve. The bicaval approach has been utilized by centers, which enables the preservation of normal atrial morphology, sinus node, and valvular function [52]. There has been an evolution of surgical techniques to explore partial heart transplantation (PHT), where only the heart valves, rather than the entire heart, are transplanted [53]. For patients with unrepairable valvular pathologies, PHT provides an avenue for valve replacement for replacing dysfunctional valves. Over 30 clinical partial heart transplants have been performed to date [54]. The first human PHT was completed in 2022 for a neonate with persistent truncus arteriosus and irreparable truncal valve dysfunction with follow-up echocardiography at age 14 months showing no obstruction and no insufficiency of the transplanted aortic and pulmonary valves [55]. The technique currently utilizes living homografts that contain viable cells, which enable the homograft to grow and self-repair, as opposed to conventional cadaver homografts [54]. Due to this, prospects of PHT will rely on compatible donor grafts and immunosuppressive therapy.

4. Future Frontiers

4.1 ABO-Incompatible Transplantation Evolution

With organ transplantation technique standardization, it was widely assumed that organs should be matched according to ABO blood types. After all, the deleterious consequences of mismatched blood transfusions were well-documented. If blood groups needed to be matched for transfusions, it stood to reason that solid organs should be matched as well to minimize these risks. Moreover, organ transplantation itself imposes significant physiological stressors, including reperfusion injury and immune responses to donor human leukocyte antigen (HLA) and ABO antigens. These stressors activate the complement system, leading to a hyperacute rejection within minutes [56].

However, ABO antigens differ from HLA antigens due to their polysaccharide structure and infants lack the immunological maturity to mount an effective response to polysaccharide antigens. As a result, they do not develop blood group antibodies until six months of age [57]. Given that infants born with severe congenital defects had an inferior prognosis, West *et al*. [57] investigated the outcomes of 10 intentional ABO-incompatible heart transplants performed between 1996 and 2000. Their protocol involved infants being serially tested for the presence of anti-A and anti-B antibodies before, during, and after the transplantation procedure. During the implantation operation, the only procedure performed for antibody removal was plasma exchange. The infants were put on the standard triple immunosuppressive regime which does not differ from the current regimen used today of a calcineurin inhibitor (tacrolimus or cyclosporine), a purine synthesis inhibitor (like mycophenolate mofetil or azathioprine), and prednisone. The infants were then surveyed for rejection at 3–4 weeks through an endomyocardial biopsy. The researchers were able to achieve an 80% survival rate, with two early mortalities unrelated to ABO incompatibility and a reduction in waiting-list mortality from 56% to 7%.

An extensive multicenter study in 2013 by Urschel *et al*. [58] further validated the safety and efficacy of ABO-incompatible heart transplantation for young patients with and without higher pre-transplant isohemagglutinin titers. The study, involving 58 transplants across six centers, demonstrated excellent graft survival rates of 100%, 96%, and 69% at 1, 5, and 10 years, respectively, with no graft loss attributed to ABO incompatibility. Following transplant, most children showed persistently low or absent antibody titers against the donor blood group, indicating a unique antigen-specific tolerance. Rejection episodes were rare, and standard immunosuppressive regimens like calcineurin inhibitors and antiproliferative agents prevented rejection [58]. Since then, ABO incompatible transplantation has evolved significantly due to advancements in antibody-mediated therapies that mitigate the risk of hyperacute rejection and improve graft survival. Modern immunosuppressive strategies, including more targeted B-cell depletion and refined plasma exchange protocols, have further enhanced post-transplant outcomes. Studies have demonstrated that many ABO-incompatible recipients develop long-term tolerance to donor blood group antigens, reducing the need for aggressive antibody removal and making ABO-incompatible transplantation a viable option even for older pediatric patients [59].

These advancements have led to a growing acceptance of ABO-incompatible heart transplantation worldwide, with some centers expanding eligibility criteria beyond traditional age and antibody titer limits. Long-term survival rates continue to improve, reinforcing the potential of ABO-incompatible transplantation to address the persistent donor organ shortage in pediatric populations. As research progresses, further refinements in immune monitoring and personalized immunosuppressive regimens may enhance outcomes and broaden the application of ABO-incompatible transplantation in clinical practice.

4.2 Xenotransplantation

One of the promising new avenues to address the ever-present shortage of donors is xenotransplantation. Xenotransplantation refers to the transplantation of organs, tissues, or cells from nonhuman species into humans. This innovative medical practice aims to address the critical shortage of human organs available for transplantation, which has become increasingly urgent due to rising demand from an aging population and chronic diseases [60]. The first ever xenotransplantation was performed in 1984 by Dr. Leonard Bailey on Stephanie Fae Beauclair, an infant with hypoplastic left heart syndrome, with a baboon heart [61,62]. The procedure although ultimately unsuccessful, marked a significant milestone in the field of cardiac transplantation and it would ultimately lead to the world's first ever successful infant to undergo xenotransplantation. Eventually, in January 2022, University of Maryland performed cardiac xenotransplantation in a 57-year-old man with end-stage heart failure and ineligibility for allotransplantation, from a genetically modified pig [63,64]. The genetic modifications included deletions of three xenogenic carbohydrate antigens (Galactose-α-1,3-galactose KO, β1,4-Nacetylgalactosyltransferase KO, CMP-N-acetylneuraminic acid hydroxylase KO, Growth Hormone Receptor Knockout) to reduce hyperacute rejection, insertion of six human genes (CD46, Delay Accelerating Factor, Endothelial Cell Protein C Receptor, Thrombomodulin, Hemeoxygenase-1, CD47) to protect against complement activation, inflammation, and coagulation, and deletion of the growth hormone receptor gene to prevent excessive organ growth [64]. The patient was supported with a novel immunosuppressive regimen, including a CD40–CD154 pathway blocker, which had proven effective in preclinical models [64]. Feasibility of xenotransplantation was evidenced by the graft functioning for 47 days. However, progressive myocardial stiffness, capillary damage, and increased anti-pig antibodies (likely related to both immune-mediated injury and porcine cytomegalovirus infection) led to graft dysfunction and ultimately the patient's death [64]. Building on the prior experience, compassionate use cases and the approval of expanded access protocols by regulatory agencies have enabled further exploration of cardiac xenotransplantation in humans. In the early clinical trials, the '10-gene pigs' have been used [65]. Recent preclinical studies in non-human primates have demonstrated survival of orthotopic cardiac xenografts for up to nine months [65]. Despite these advances, significant challenges remain. Immune suppression remains a critical hurdle, with the need for optimal drug combinations to control antibody-mediated rejection and for regulatory approval of novel agents. Physiological challenges, such as the risk of graft overgrowth and the impact of recipient comorbidities, also require careful consideration.

Xenotransplantation also poses several ethical challenges. There is risk of zoonotic disease transmission—infections that could pass from pigs to humans, potentially affecting not only recipients but also the broader public [66,67]. This necessitates rigorous bio-surveillance protocols for recipients and possibly their close contacts [66,67]. Patient selection is another critical ethical issue. Early clinical cases have relied on compassionate use pathways for patients with no other treatment options, raising concerns about informed consent and the potential for vulnerable individuals to be offered experimental treatments [68]. Animal welfare is a persistent concern, as the creation and maintenance of genetically engineered pigs for organ donation involve significant ethical considerations regarding the use and treatment of animals [67]. Additionally, there are broader societal and philosophical questions about crossing species boundaries and the long-term implications for medicine and society.

Balancing innovation with safety, equity, and respect for all stakeholders—patients, animals, and the public—

remains central to the ethical advancement of cardiac xenotransplantation. Ongoing dialogue, regulatory clarity, and transparent communication are essential as the field moves toward broader clinical application.

4.3 Bioartificial Heart Transplantation

Bioartificial heart is a theoretical alternative to transplantation or mechanical left ventricular support [69]. There have been various research studies on cardiac bioengineering. Previously published studies have reported decellularization of animal hearts and their eventual recellularization via reseeding them with cardiac and/or endothelial cells under simulated physiological conditions [69–71]. Re-cellularized whole-heart neo-scaffolds have demonstrated re-endothelialization of coronary vasculature and measurable intrinsic myocardial electrical activity; provide a promising tissue-engineering platform that may lead to future clinical strategies in the treatment of heart failure [69–71]. This *de novo* generation of bioartificial hearts by decellularization and preservation of supporting structures for their subsequent repopulation with new contractile, vascular muscle tissue could potentially entail transplantation of the "rebuilt" heart, thus, re-establishing cardiac function in the recipient [69–72].

Engineering a bioartificial heart from synthetic scaffolds and cardiac cells remains a challenge due to the heart's complex structure and function. Despite these complexities, recent advances in three-dimensional (3D) printing technology have brought new hope for the development of complex, functional bioartificial organs [73]. Currently, 3D printing is used to create patient-specific heart models from imaging data, which are valuable tools for surgical planning [73]. Recent breakthroughs include bioprinting human cardiomyocyte progenitor cells into alginate scaffolds to form viable cardiac constructs, as well as creating cardiac patches with human vascular endothelial cells and mesenchymal stromal cells [73]. The integration of living cells directly into scaffolds during the printing process is emerging as a promising long-term approach. Additionally, innovative research by Park *et al*. [74] proposes hybrid scaffolds that may incorporate compressible elements inspired by sting ray morphology, combined with patterned muscle architecture, to improve the spatial organization of contraction and enhance pumping efficiency. Whether these hybrid designs can outperform the natural heart's efficiency while offering a structurally simplified alternative remains an open question.

5. Bioethical Implications and Regulations

Pediatric heart transplantation presents unique bioethical challenges and is governed by a robust regulatory framework designed to balance medical need, justice, and respect for autonomy in the context of scarce organ resources. The most pressing ethical issues in pediatric heart transplantation center on organ scarcity and the resulting dilemmas in allocation and access [75]. With limited donor hearts available, questions arise about which children should receive priority and how to ensure fairness in the listing and selection process [75]. Utility refers to allocating organs to maximize overall benefit, while justice emphasizes fair distribution among all potential recipients [76]. Autonomy, though less directly exercised in pediatric cases due to the age of the patients, is upheld through parental informed consent and shared decision-making between families and the medical team [76].

Shared decision-making is critical, as parents act as surrogate decision-makers for their children, basing choices on the best-interest standard and the child's future well-being [76]. However, the process is complicated by the need for rapid decisions, especially when donor hearts from increased-risk donors (Public Health Service increased-risk, or PHS-IR) are offered [76]. Current policy requires separate informed consent for PHS-IR donor hearts, which can isolate parents from the clinical expertise of the transplant team at a critical moment, potentially increasing wait times and mortality risk for children who decline these offers [76]. The negligible difference in outcomes between PHS-IR and standard-risk donor hearts further complicates ethical decision-making, highlighting the need for nuanced, evidence-based counseling and transparency.

Other ethical considerations include the psychosocial impact on children and families, quality of life after transplantation, and end-of-life care decisions [77]. The assessment of candidates with genetic anomalies or developmental delay also raises questions about equity and the value placed on different lives. Referral patterns and access to transplant centers can introduce disparities based on geography, socioeconomic status, or institutional policies, underscoring the importance of equitable access and regulatory oversight [77].

The regulatory environment for pediatric heart transplantation is designed to ensure fairness, transparency, and accountability. In the United States, the Organ Procurement and Transplantation Network (OPTN) is responsible for developing policies that promote equitable allocation of deceased donor organs, as required by the Final Rule [78]. The OPTN's National Heart Review Board (NHRB) for Pediatrics provides peer review of exception requests for pediatric candidates whose medical urgency is not adequately reflected by standard listing criteria [78,79]. This process aims to prevent bias and ensure that all children have a fair chance at receiving a transplant based on medical need, not on extraneous factors. The NHRB includes representatives from pediatric heart transplant programs, with strict guidelines for confidentiality, conflict of interest, and timely review of applications. Policies are continuously updated to reflect advances in medical knowledge and evolving ethical standards. For example, the OPTN has issued guidance on the use of pediatric heart exceptions, detailing the fac-

tors reviewers should consider when evaluating requests for exceptions to standard allocation rules [79].

Pediatric heart transplantation is a life-saving but ethically complex intervention. The primary bioethical implications revolve around organ scarcity, justice in allocation, and the role of surrogate decision-making. Regulatory frameworks, such as those established by the OPTN and NHRB, are essential for ensuring that these procedures are conducted fairly and transparently, with ongoing attention to the evolving needs of children and families. Balancing the principles of utility, justice, and respect for autonomy remains central to both ethical analysis and regulatory practice in this field.

6. Conclusion

Over the last few decades, pediatric heart transplantation has undergone various stages of progression. The current decade has involved significant advancements that include donor source expansion with DCD hearts, further advancements in immunosuppression, organ preservation innovations such as the development of *ex-vivo* perfusion systems, and emerging surgical techniques such as partial heart transplantation. An evolving frontier is ABO-incompatible transplantation, and future research is exploring ABO-incompatible and bioartificial transplantation along with xenotransplantation.

Author Contributions

LE, LS, AF, HJ, BA, SH, AZ, RHL and TKR contributed equally to the design, draft, writing, and review of this manuscript. TKR also provided oversight as the senior author of the review article. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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