Xenotransplantation and Pediatric Ethics Issues

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Introduction

In 1984, an infant with hypoplastic left heart syndrome would become the first infant to receive a xenograft—a baboon heart. "Baby Fae," as the infant was known, would die 21 days after the transplant of heart failure from her body's immune system rejecting the xenograft. The Baby Fae event would prove to be a landmark in the field of xenotransplantation (XTx) and would spur a flurry of writings on the ethics of XTx, including pediatric XTx and experimental therapies in a pediatric population. To date, Baby Fae is the only known pediatric recipient of a cardiac xenograft.

XTx, which has since the time of Baby Fae moved to a pig model, has been proposed as a potential therapy in children to help alleviate the critical organ shortage that exists. Currently, nearly 2000 children in the United States (US) are on an organ transplant waiting list.[1] For children under the age of 1, the majority of patients on the waitlist are in need of a heart or liver. For children between 1 and 18, most are waiting for a kidney.

[1] https://www.donatelife.net/wp-content/uploads/2016/06/2021-NPTW-Donation-and-Transplantation-Statistics-FINAL-3.4.21.pdf.

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Some commentators have proposed that initial clinical trials of XTx will focus on adult kidney xenografts, with pediatric cardiac transplants for children with congenital heart disease (CHD) not too far behind [1]. Ethical concerns arise in the pediatric population in regard to XTx due to the potential of performing experimental therapeutic research in this population without having first conducted trials in an adult population, which is not recommended by governing bodies such as the U.S. Food and Drug Administration (FDA) and the World Health Organization (WHO). XTx may not be as needed for adults with heart failure as there are other clinical alternatives that currently hold longer survival than pig xenografts, however these clinical alternatives have poor outcomes in pediatric patients with CHD. Therefore, testing XTx in adults before children would seem infeasible and pose ethical issues. While this is an issue in any medical intervention involving children, XTx represents a special case. In XTx, it has been proposed that recipients of a xenograft should be monitored for the remainder of their life to ensure they have not acquired a xenozoonotic infection. This chapter will explore these challenges of advancing XTx—particularly heart xenografts—in the pediatric population as clinical trials are likely to begin soon after adult kidney xenograft clinical trials. We will attempt at providing some solutions to the issues we have identified.

Informed Consent

Informed consent (IC) is considered one of the most important elements of research. While IC is much more than a document, it does oftentimes, especially in the research context, result in a document that a research subject and/or their surrogate must agree to and then sign. The IC document is a tool meant to inform the potential subject of all the activities they would have to undergo in order to participate, as well as the risks and benefits associated with participation [2]. In the United States (US), IC documents are reviewed and approved by institutional review boards (IRBs) and can vary, but all must contain and address the minimum required elements established by the US Department of Health and Human Services (HHS) under Title 45 Code of Federal Regulations part 46 [3]. The basic elements from the HHS and the ethical challenges that kidney XTx would impose on these elements have previously been described elsewhere and would apply also to children [2]. In addition to the basic elements, section subpart D only applies to research in children [3, 4], including instructions surrounding assent, risk category determinations, children who are wards of the State or other agencies, and possible additional reviews and approvals beyond IRBs by HHS for certain risk determinations. Challenges for parental/guardian consent to this particular vulnerable population have not been discussed previously.

It is highly unlikely that XTx research in children will be classified as minimal risk, especially in the absence of cardiac clinical trials in adults. Thus, the clinical trials will likely fall into risk determination categories that involve greater than minimal risk to the child and vary based on whether or not the argument can be made that there is a direct benefit to the child, or if it is only to provide scientific

knowledge and possibly advance the field. Lastly, if the IRB does not classify the research into any of the aforementioned categories, it would require additional HHS approval beyond the institutional IRB level. This instance is applicable to research that is not otherwise approvable but is an opportunity to alleviate a serious problem affecting the health or welfare of children. Although there is the argument that children with CHD pose a unique opportunity for XTx due to their immature immune system that would decrease their chance of rejection [5], coupled with the worse outcomes they face over adults and other solid organ waitlists/mortalities, it is unknown which category IRBs will determine the research application. Before this can happen, there would need to be details of the study design and development of pre-clinical trials for cardiac XTx data that can be generalizable for children. It is also unknown if clinical trials will explore the use of cardiac XTx as a bridge to allotransplant to increase waitlist survival, or as an alternative to allotransplantation. If XTx is only used as a bridge, IRBs may differ on perceived benefits and risks for extending waitlist survival via XTx compared to other clinical alternatives; for example the comparison of using Berlin hearts or if they weigh the risk of exploring the use of XTx for children with CHD lower than their current risk and mortality faced by their disease or waitlist. It would also be interesting to see how HHS would weigh these risks if it were to become applicable [4].

Subpart D also provides additional provisions about age when a child can consent for themselves, assent for children, and parental permissions. These ages for consent and assent by the child vary by state, a child's maturity, and psychological state. For cardiac XTx for children with CHD it is most likely that children will be too young to consent or assent for research or clinical treatments. Most often, parents and/or legally authorized representatives (LAR) are the medical decision makers. Nevertheless, the discussion for when the child should be involved and allowed to consent/assent is required. At what point should the child choose whether they want to wait for a human organ or accept a genetically engineered pig organ? What if a child does not want to accept the organ but the parents do? The answer to age involvement may also be influenced if it is a life sparing organ (heart) vs. an organ that has other clinical organ replacement alternatives, like dialysis for kidneys. If the child was too young to provide an opinion to accept a xenograft, should they be re-consented at some point? If so, when? It has been discussed that a subject would potentially not lose their place on the waitlist if they accept a xenograft [2]. When can the child decide if they want to remove a theoretically functioning xenograft and undergo a second surgery to replace it with a human organ?

This leads to the challenge of the child's ability and right to withdraw from the XTx research. When can a child assess the implications of lifelong treatment and monitoring (to monitor for xenozoonotic risks)? [6] Non-adherence to needed medications to prevent transplant rejection in pediatrics are even faced in allotransplantation. A study by Oliva et al. reported that 9% of pediatric heart transplant recipients reported non-adherence and that this most commonly occurred during adolescence (15 years old) [7]. Non-adherence results in poor outcomes, rejection and death in some instances, and it is very likely that cardiac XTx will face non-adherence challenges by children as well. How will these be addressed? Could non-adherence be

higher since an adolescent may have more negative feelings about having a pig heart in their bodies compared to a human heart? Exploring the age of children involvement and what adolescents may think about cardiac and other organ XTx and the demands of participating in such clinical trials may be warranted.

Research on Pediatric Perspectives and Ethical Issues

To date there have been few studies that explore the viewpoints of either parents/guardians of having their child receive a xenograft, or a mature minor perspective (i.e., a minor who may be able to be treated as an adult for certain procedures). A recent meta-analysis on public perception toward XTx concluded that there is insufficient information known about patient attitudes in particular [8]. This can be extended to the pediatric population in which there is generally not much known regarding how parents/guardians or mature minors feel.

There are two studies that have attempted to assess the attitudes of various stakeholders for the use of cardiac XTx for children with CHD [9, 10]. Assuming XTx has similar outcomes to allotransplantation, acceptance among congenital heart surgeons and pediatric cardiologists is high (>80%). However, this high acceptance dropped if the outcomes were not comparable to allotransplantation even if the xenograft was only used as a bridge to an allograft. However, if the xenograft is effective then most participants would not remove it even if a human heart became available. When parents of children with CHD were surveyed in another study using a Likert scale survey, they too showed a high acceptance (70–80%) for XTx if results were similar to allotransplantation. Similar to other studies, acceptance dropped if the results were not comparable to allotransplantation.

In one focus group study with parents of children with CHD, there was near unanimous agreement that they would certainly accept a pig heart in order to save their child [11]. Further, parents also seemed comfortable in choosing XTx as a clinical option if their physician and/or healthcare team thought it was a good option. There seemed to be an opportunity that if educated on XTx their acceptance could possibly increase. The approval and advancement of kidney XTx may exceed that of CHD in adults but it would be interesting to see if kidney XTx reaches use in pediatric populations with end stage renal disease (ESRD) before cardiac XTx does for children with CHD. If this is the case, what would parent attitudes be of accepting a kidney xenograft for their child? Do parents feel the same way about kidney XTx as cardiac XTx given the renal replacement therapies available? This is something that has not been addressed in the literature and would be worthwhile to start exploring.

The studies on CHD attitudes among parents also showed two important factors that may influence acceptance: religion and psychosocial concerns. In one study, nearly 50% of surveyed parents of a child with CHD stated that religious beliefs were always or often influential in their decision-making [10]. Regression analysis indicated that those whose religious beliefs have a greater impact on their medical decision-making were less likely to accept a xenograft. While there has been at least

one significant publication from the Catholic Church on the permissibility of XTx [12], the theological literature from other faith groups on XTx is sparse and mostly has come from academic theologians. While an entire section of this volume is dedicated to exploring the religious viewpoints toward xenotransplantation, there is also a noticeable lack of commentary on organ transplantation from a religious perspective that differentiates between pediatric and adult recipients. This could be an area for major world religions to begin considering how their faith group might respond.

Parents seem to be concerned with the way that being a pig organ recipient would affect their child socially. Even patients who receive human organs face psychological challenges and body image challenges from receiving an allograft. One could assume that a child as they grow may also be faced with similar concerns. Similar to allotransplantation, the support of counseling and therapy would be advisable. Bullying is a common parental concern for any child these days, and the effects of a child being bullied for having a pig heart may be real as pigs hold a negative and dirty connotation in many societies. Pigs are dirty animals and the word 'pig' is often used as an insult. What exactly these parental concerns are and how best to address them while providing the best support for children if XTx would become an option for them is needed.

Experimental Therapeutic Research in Pediatrics

In the development of therapeutic options for the pediatric population, investigators must avoid two harms: (1) exploiting this vulnerable population in research, as a tarnished history of pediatric research shows, and (2) excluding children from research due to fear of harming a vulnerable population. The pediatric population has been called "therapeutic orphans" for this reason, because children have either been denied access to new medications or exposed to medications that have only been evaluated on the adult population [13]. Additionally, it can, understandingly, be difficult for parents to allow their children to participate in novel therapies from fear of individuals experimenting with their child. The paradigm is shifting from a perspective that protects children from research by exclusion to a "cautious advocacy" that values the participation of children in research with proper consideration to risks and benefits and scientific necessity [14].

Clinical trials in a pediatric population can be a challenging endeavor. Conducting trials in children is often more difficult than in adults due to the increased cost and liability along with decreased commercial interest, especially for the pharmaceutical industry. Yet, children need high-quality clinical trials too before a new therapy is used. Or, to paraphrase Klassen et al., children are not little adults [15], thus generalizability from adult trials sometimes is limited. They are a heterogeneous group ranging from preterm neonates to post-pubertal adolescents (or mature minors) and often experience different outcomes with the same drug [13, 15, 16]. Children can have physiological differences dependent on the age or developmental stage that can affect a clinical therapy or outcome. There are additional clinical goals in pediatric medicine of getting the patients to adolescence and adulthood

rather than simply maintaining or regaining previous quality of life [16]. Similarly, in clinical trials for adults, success is achieved by delaying the inevitable, whereas for children, the objective is to find a treatment that can offer as "normal" quality of life as possible. These differences suggest an ethical rationale for not relying solely on adult outcomes, which often lack generalizability for the pediatric population, but also the establishment of independent pediatric clinical research and rigorous clinical trials in pediatric patients [16].

The field of pediatric cardiology and congenital heart surgery has seen major advancements in the past 50 years, with many procedures that were experimental not long ago now part of common practice [17, 18]. Successful congenital cardiac repairs were rarely performed before the advent of the early heart-lung machine, which was in the early stages of development in the 1950s. Early attempts at open-heart surgery with a heart-lung machine at that time had a high mortality rate [17]. Over the next 20 years, practice changed to recognize the benefit of early surgical intervention in infants rather than delaying repairs for 5–7 years [17]. Arterial switch operations on infants with transposition of the great arteries and ventricular septal defects were being performed successfully by the late 1970s, thus marking a new era of early primary repair for complex congenital heart defects. The first successful infant heart allotransplant was in 1984, and post-transplant survival rates continue to improve every year [19, 20]. The year after Baby Fae died, the same surgeon transplanted a human heart to another HLHS newborn who is still alive today [19]. Although complex CHDs were uniformly fatal at the beginning of the twentieth century, the field has reached an era where skilled individuals and rapidly improving technology have substantially improved long-term survival for most CHDs [16, 18].

Recently, an adult man in Maryland received a porcine heart, provisionally allowed by the FDA through compassionate use [21]. The first approved pediatric cardiac XTx instances may also be through compassionate use allowances. Although the implication is that the child would be extremely sick, so were many of the first pediatric cardiac allotransplant recipients and pediatric patients who received the first CHD repairs. In 2021, a new organ preservation technology was used under compassionate use authorization in a 14-year-old patient to perform "donation after circulatory death" (DCD) heart transplant, just 2 years after it was first used under the same terms for an adult transplant [22]. Subsequently, the technology was tested in clinical trials and gained FDA approval for use in adults the same week the pediatric patient was transplanted.

In considering the prospect of cardiac XTx for the pediatric population, with the need for hearts for this population being greater than adults, how do we begin to conduct these clinical trials? What pediatric age group would be appropriate? Somehow we must reconcile the commitment to not treat children as little adults with the acknowledgement that if this is to become a clinical option, someone will have to go first. In some ways, the first heart transplants probably carried more risk than this era's first xenotransplants will—established immunosuppressant regiments, experienced multidisciplinary teams and pig-to-baboon animal studies all

suggest higher preparedness. However, the results of the Maryland patient show that so many factors are yet unknown [21].

To summarize, experimental therapeutic options for the pediatric population are tested for safety and efficacy first, and perhaps approved for use in the adult population before pediatric. Next, or perhaps concurrently, testing for cardiac XTx is done cautiously, as compassionate use in the absence of a suitable allograft and other life-sustaining measures are not thought to be adequate, and then in clinical trials to test that the therapeutic drug or technology is also tolerated and successful in the pediatric population. Testing the feasibility for cardiac XTx in adults knowing that their age group holds better clinical options and that results from adult cardiac XTx may have limited generalizability for children may be not be appropriate. It may also be important to consider that advancement should happen through formal clinical trials with clear inclusion/exclusion criteria and not with isolated experiments blanketed by compassionate use for desperate patients and dire clinical scenarios.

Conclusion

XTx is making scientific advancements to become a clinical reality. After approval for adult kidney XTx it is thought that cardiac XTx for children with CHD will follow shortly thereafter. Additionally if kidney xenografts are approved for adults with ESRD it would be unethical to deprive children in a similar transplant need to this clinical option. Therefore, we must acknowledge the unique challenges that potential pediatric recipients of a xenograft could face such as those during the consent process and the psychosocial implications. Lastly, the risk they will face if involved in testing a new technology or the non-benefit if left out of the initial clinical trials must be considered. Children with CHD, specifically those under the age of one who are in need of a heart, face the highest waitlist mortality. Children provide an opportunity over adults to decrease the years of potential life loss if saved. Studies and assessments that involve important stakeholders that can help best prepare for inclusion of children in XTx in order to best protect them while attempting to benefit them is crucial.

References

1. Hurst DJ, Padilla LA, Cooper DKC, Cleveland DC, Paris W. Clinical trials of pediatric cardiac xenotransplantation. Am J Transplant. 2021;21(1):433–4.
2. Padilla LA, Hurst D, Maxwell K, Gawlowicz K, Paris W, Cleveland D, Cooper DKC. Informed consent for potential recipients of pig kidney xenotransplantation in the United States. Transplantation. 2022;106(9):1754–62. https://doi.org/10.1097/TP.0000000000004144. Epub ahead of print.
3. US Department of Health & Human Services. Office for human research protections. General requirements for informed consent. hhs.gov. https://www.hhs.gov/ohrp/regulations-and-policy/regulations/regulatory-text/index.html#46.116. Published July 14, 2019. Accessed 10 Sept 2021

4. US Department of Health & Human Services. Research with children FAQs. In: Office for human research protections. hhs.gov. https://www.hhs.gov/ohrp/regulations-and-policy/guidance/faq/children-research/index.html. Accessed 10 Sept 2021.
5. Li Q, Hara H, Banks CA, Yamamoto T, Ayares D, Mauchley DC, Dabal RJ, Padilla L, Carlo WF, Rhodes LA, Cooper DKC, Cleveland DC. Anti-pig antibody in infants: can a genetically engineered pig heart bridge to allotransplantation? Ann Thorac Surg. 2020;109(4):1268–73. https://doi.org/10.1016/j.athoracsur.2019.08.061. Epub 2019 Sep 30.
6. Hurst DJ, Padilla LA, Walters W, Hunter JM, Cooper DKC, Eckhoff DM, Cleveland DC, Paris W. Paediatric xenotransplantation clinical trials and the right to withdraw. J Med Ethics. 2019;46(5):311–5. https://doi.org/10.1136/medethics-2019-105668.
7. Oliva M, Singh TP, Gauvreau K, Vanderpluym CJ, Bastardi HJ, Almond CS. Impact of medication non-adherence on survival after pediatric heart transplantation in the U.S.A. J Heart Lung Transplant. 2013;32(9):881–8. https://doi.org/10.1016/j.healun.2013.03.008.
8. Mitchell C, Lipps A, Padilla L, Werkheiser Z, Cooper DKC, Paris W. Meta-analysis of public perception toward xenotransplantation. Xenotransplantation. 2020;27(4):e12583.
9. Padilla L, Sorabella R, Carlo W, et al. Attitudes to cardiac xenotransplantation by pediatric heart surgeons and physicians. World J Pediatr Congenit Heart Surg. 2020;11(4):426–30.
10. Padilla LA, Rhodes L, Sorabella RA, et al. Attitudes toward xenotransplantation: a survey of parents and pediatric cardiac providers. Pediatr Transplant. 2021;25(2):e13851.
11. Hurst DJ, Padilla LA, Cooper DKC, Paris W. Factors influencing attitudes toward xenotransplantation clinical trials: a report of focus group studies. Xenotransplantation. 2021;28(4):e12684.
12. Pontifical Academy for Life. Prospects for xenotransplantation: scientific and ethical considerations. Vatican. http://www.vatican.va/roman_curia/pontifical_academies/acdlife/documents/rc_pa_acdlife_doc_20010926_xenotrapianti_en.html. Accessed 26 May 2020.
13. Joseph PD, Craig JC, Caldwell PH. Clinical trials in children. Br J Clin Pharmacol. 2015;79(3):357–69. https://doi.org/10.1111/bcp.12305.
14. Roth-Cline M, Gerson J, Bright P, Lee CS, Nelson RM. Ethical considerations in conducting Pediatric research. In: Seyberth H, Rane A, Schwab M, editors. Pediatric clinical pharmacology. Handbook of experimental pharmacology, vol. 205. Berlin, Heidelberg: Springer; 2011. https://doi.org/10.1007/978-3-642-20195-0_11.
15. Klassen TP, Hartling L, Craig JC, Offringa M. Children are not just small adults: the urgent need for high-quality trial evidence in children. PLoS Med. 2008;5(8):e172. https://doi.org/10.1371/journal.pmed.0050172.
16. Gidding SS. The importance of randomized controlled trials in pediatric cardiology. JAMA. 2007;298(10):1214–6. https://doi.org/10.1001/jama.298.10.1214.
17. Castañeda A. Congenital heart disease: a surgical-historical perspective. Ann Thorac Surg. 2005;79(6):S2217–20. https://doi.org/10.1016/j.athoracsur.2005.03.031.
18. Mayo Clinic. Congenital heart disease: the first 50 years … the next 50 years. Mayo clinic cardiovascular diseases and cardiac surgery. 2019. https://www.mayoclinic.org/medical-professionals/cardiovascular-diseases/news/congenital-heart-disease-the-first-50-years-the-next-50-years/mac-20453657
19. Chinnock RE, Bailey LL. Heart transplantation for congenital heart disease in the first year of life. Curr Cardiol Rev. 2011;7(2):72–84. https://doi.org/10.2174/157340311797484231.
20. Dipchand AI. Current state of pediatric cardiac transplantation. Ann Cardiothorac Surg. 2018;7(1):31–55. https://doi.org/10.21037/acs.2018.01.07.
21. Griffith BP, Goerlich CE, Singh AK, Rothblatt M, Lau CL, Shah A, Lorber M, Grazioli A, Saharia KK, Hong SN, Joseph SM, Ayares D, Mohiuddin MM. Genetically modified porcine-to-human cardiac xenotransplantation. N Engl J Med. 2022;387(1):35–44. https://doi.org/10.1056/NEJMoa2201422. Epub 2022 Jun 22.
22. Duke Health. Duke performs first U.S. pediatric heart transplant using new method. Duke health news & media. 2021. https://corporate.dukehealth.org/news/duke-performs-first-us-pediatric-heart-transplant-using-new-method