Ethical Considerations in Patients with Extracardiac or Genetic Anomalies

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1 Introduction

Patients with congenital heart disease (CHD) often have other comorbidities including extracardiac and genetic anomalies. Epidemiological studies have shown that a genetic or environmental cause can be identified in up to 20–30% of CHD cases [1–7]. The presence of extracardiac or genetic anomalies can negatively impact outcomes in patients with CHD and lead to increased hospital stay, higher in-hospital mortality, unplanned reoperations, and diminished late survival, especially if the extracardiac anomalies are significant or if the heart surgery is complex [4, 8–12]. However, repair or intervention for CHD patients with extracardiac anomalies does not always pose higher risks [13]. Therefore, recognition and evaluation of anomalies is important to assure proper prognostication, appropriate family counseling, and fully informed consent.

As genetic screening practices evolve and more centers perform broad microarray and whole genome sequencing, genetic anomalies with a known phenotype and those with "unknown significance" will be increasingly reported in patients with CHD [14–16]. Many cases of CHD surgery occur in patients with mild renal or genitourinary anomalies and the analysis of whether to proceed with surgery is not impacted much by these types of extracardiac anomalies. Sometimes the extracardiac or genetic anomaly, however, is substantial enough to cause the timing of CHD surgery to be altered (i.e. delaying full repair of Tetralogy of Fallot in a patient with

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a large gastroschisis). Other times, conflicts may arise about what is in the best interest of the child, appropriate ethical justifications for not offering surgery, and how to balance justice and societal burdens when the child has significant extracardiac anomalies that may limit his or her lifespan appreciably and/or impact quality of life.

2 Ethical Issues and Extracardiac Anomalies

Several justifications have been given for withholding surgery for some patients with extracardiac or genetic anomalies including: (1) harm to the infant during and after surgery; (2) quality of life after surgery; (3) lack of data to support that surgery improves the overall prognosis; (4) potential of providing false hope or unrealistic expectations for the family; and (5) concerns about improper allocation of time and resources [17–21].

While these concerns are undoubtedly important, they are points that should be considered for *any* cardiac patient, not just for those patients with extracardiac anomalies. For example, it may be ethical to withhold surgery for a patient with recurrent pulmonary vein stenosis who does not have any extracardiac anomalies for precisely the same reasons listed above. Our profession must be careful to use the justifications listed above fairly and consistently when considering *all* patients, and not just those with extracardiac or genetic anomalies. It is important to understand the historical perspective and changes in the types of medical care offered to children born with genetic and other anomalies over the past half century to better inform how we make those decisions in the modern era.

3 Historical Perspectives

Prior to the 1980s, many children born with disabilities were denied lifesaving surgeries and the decisions were largely left to the physician and families of these infants [22, 23]. The social and political landscape, however, changed after an important case in 1982 when a baby boy (Baby Doe) was born in Bloomington, Indiana with trisomy 21 and tracheoesophageal fistula. If not surgically corrected, Baby Doe would die from this anomaly. Baby Doe's mother's obstetrician recommended that the family not pursue surgery, citing a 50% change of survival and poor long-term neurodevelopment. The parents agreed and declined surgical intervention. The pediatrician and family physician opposed this plan as they believed that the family was given flawed statistics about survival and prognosis. These physicians found attorneys and couples who were willing to adopt the child. The local court, however, deferred to the parents' decision and upheld their right to make this decision for their baby. Baby Doe died of dehydration and pneumonia on day of life 6 before the case could be appealed [24].

The Surgeon General at the time, C. Everett Koop, was furious. He had been chief of surgery at Children's Hospital of Philadelphia and had a nearly 100%

success rate with repair of tracheoesophageal fistulas. He declared that the family's decision to forego treatment was based purely on the potential for future disability for the child and called it discrimination against children with disabilities [24]. In addition, public outcry about the case was exceptionally loud from pro-life and disability rights groups [25]. In response, the Reagan administration ordered Koop and the head of Department of Health and Human Services to notify healthcare workers that they could lose federal funding if they did not provide treatment to handicapped infants under Section 504 of the Rehabilitation Act of 1973.

In 1983, to help enforce these regulations, the Department of Health and Human Services set up telephone hotlines and required posting of the "Baby Doe rules" in all hospital nurseries and required that any person who had knowledge that a handicapped infant was being discriminatorily denied food or customary medical care should immediately contact the Handicapped Infant Hotline. These initial regulations were struck down by the Supreme Court in 1986 because the Reagan administration's interpretation of Section 504 was declared incorrect [26], but revised Baby Doe rules were passed by congress in 1984 and became part of the amendment to the Child Abuse Prevention and Treatment Act (CAPTA) [27].

The CAPTA amendment Baby Doe rules stated that a physician could not withhold medically indicated treatment for an infant unless: (1) the infant is chronically and irreversibly comatose, (2) treatment would merely prolong dying, not be effective in ameliorating or correcting all of the infant's life-threatening conditions, or otherwise be futile in terms of survival of the infant, or (3) treatment would be virtually futile in terms of survival of the infant and the treatment itself under such circumstances would be inhumane [27]. Notably, these rules do not allow for the infant's quality of life to be taken into consideration and they do not mention the "best interest" of the infant.

Around the same time as the Baby Doe rules were promulgated, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research issued a report that reviewed the standard that should be used when a surrogate makes decisions on behalf of someone who cannot speak for themselves. When there is no history to provide insight as to how that person may have wanted to proceed (as is always the case for infants), the Commission recommended that the best interest standard be used [28]. In the Commission's report entitled "Deciding to Forego Life-Sustaining Treatment" they specifically stated that "relief of suffering, the preservation or restoration of functioning, and the quality, as well as, the extent of life sustained" could be taken into account when making such decisions [29]. With regard to infants, the report stated that parents "should be surrogates for seriously ill newborns" unless their choice is "clearly against the infant's best interests." The report also emphasized that decision-makers should have access to "the most accurate and up-to-date information" when making their decisions [29]. This report emphasizes the ethical principles that are routinely employed in modern pediatric medicine, including the best interest standard and the importance of informed consent based on accurate information.

The American Academy of Pediatrics (AAP) addressed the conflict between the Baby Doe rules and the reports of the President's Commission by endorsing the best

interest standard. The AAP's Infant Bioethics Task Force and Consultants issued the "Guidelines for Infant Bioethics Committees" and recommended that ethics consultation and review be offered when making decisions to forego life-sustaining treatments for infants. The AAP's Committee on Fetus and Newborn issued guidelines on non-initiation or withdrawal of treatment for high-risk newborns in 1995, which were then revised in 2007 [30]. The statement supports foregoing intensive care in cases that were likely fatal or had a high risk for severe morbidity. Importantly, they deferred to parental decision-making with the best interest standard in cases where "the prognosis is uncertain but likely to be very poor and survival may be associated a diminished quality of life for the child."

The AAP Committee's final recommendations included:

1. Decisions about non-initiation or withdrawal of intensive care should be made by the health care team and the parents of a high-risk infant working together. This approach requires honest and open communication. Ongoing evaluation of the condition and prognosis of the high-risk infant is essential, and the physician, as the spokesperson for the health care team, must convey this information accurately and openly to the parents of the infant.
2. Parents should be active participants in the decision-making process concerning the treatment of severely ill infants.
3. Compassionate basic care to ensure comfort must be provided to all infants, including those for whom intensive care is not being provided.
4. The decision to initiate or continue intensive care should be based only on the judgment that the infant will benefit from the intensive care. It is inappropriate for life-prolonging treatment to be continued when the condition is incompatible with life or when the treatment is judged to be harmful, of no benefit, or futile [30].

The historical context provides a pathway on how to proceed with infants with CHD defects and extracardiac or genetic anomalies. Just as the AAP recommends using the best interest standard for decisions surrounding non-initiation of intensive care or withdrawal of intensive care for *any* medical condition, the cardiologist and cardiac surgeon should use a similar standard when deciding whether to offer cardiac surgery to an infant with significant anomalies that may make surgical outcomes worse or decrease the benefits that the surgical intervention may produce.

The subjective nature of the best interest standard can lead to conflicts among physicians and between parents and phyisicans. The AAP statement on "Guidance on Forgoing Life Sustaining Medical Treatment" states that "when the balance of benefits and burdens to the child shifts, forgoing life-sustaining medical treatment is ethically supportable and advisable" [31]. The AAP also offers guidance when there is disagreement between the care team and the family decision-makers or between family members and suggests that the clinician: (1) Use principles of negotiation and conflict resolution and support from pastoral care providers and consultants in palliative care or ethics; and (2) Allow for reasonable accommodation for the timing of forgoing life-sustaining medical treatment to allow family members to gather but take utmost care to avoid prolonging the patient's suffering [31].

Furthermore, it may be ethically justifiable to forgo life-sustaining medical treatment despite family objections in rare circumstances of extreme burden of treatment with no benefit to the patient beyond postponement of death [31].

Clearly, the way that we treat trisomy 21 has changed considerably over the past 50 years and what is considered "best interest" has evolved with changing societal views and medical outcomes. To discuss every genetic or extracardiac anomaly and combination of CHD is beyond the scope of this chapter, so trisomy 13 and 18 are used here as examples of genetic syndromes where the decision of whether or not to offer cardiac interventions is often debated. Discussion of these syndromes establishes a framework for analysis that can be used for other genetic and extracardiac anomalies.

4 Infants with Trisomy 13 and 18

Trisomy 18 is an autosomal dominant with a prevalence of one in 3000 to one in 8000 live births [32]. Many patients are diagnosed prenatally and do not survive to birth either due to elective termination or in utero demise. Infants with trisomy 18 usually have minor to major birth defects, severe psychomotor and neurocognitive disabilities, and an increased risk of mortality. The majority of CHD in these patients are septal defects and patent ductus arteriosus, although some have more complex heart disease such as hypoplastic left heart syndrome. The major causes of death for these patients are respiratory failure, apnea and heart failure from unrepaired CHD [32].

Historically, trisomy 13 and 18 were considered "incompatible with life" and death frequently occurred within the 1st year of life attributed to causes other than CHD, with 5–10% infants surviving to 1 year of age [33]. More recent data, however, show that with interventions such as congenital heart disease surgery, many infants survive longer. Several studies published in the 1990s and 2000s showed some but still low percentages of patients surviving to 5 years of life and some beyond [32, 33]. In the 2010s, a shift occurred where researchers asked whether children with trisomy 13 and 18 were not surviving because they were not being offered surgery. Several small studies showed survival in children with trisomy 13 and 18 may be longer if they received cardiac interventions [34, 35].

Kosiv et al. used the Pediatric Health Information System (PHIS) database from 2003 to 2015 and identified congenital heart disease in 91% of infants with trisomy 18 and 86% of infants with trisomy 13. These varied across the spectrum of severity. Of this group, only 7% underwent cardiac surgery but those who had surgery had better survival than those who did not [36]. The authors implied that the decision to forego surgery may be based on a mistaken belief that infants with these trisomies die regardless of any intervention [37]. Previously, the lack of data and perceived risk of inevitable death made physicians more likely to withhold surgery for CHD in this population, however these newer studies provide persuasive evidence that CHD surgery should be contemplated in some cases. Certainly, parental informed

consent about the infant mortality risk with cardiac surgery and the expected severe neurocognitive delays with these syndromes still needs to occur [37].

Peterson et al. queried the Pediatric Cardiac Care Consortium (PCCC) database between 1982 and 2008 and found that 29 of 50 patients with trisomy 13 and 69 of 121 patients with trisomy 18 (including mosaics) underwent cardiac surgery. This was one of the largest cohorts of patients with these trisomies undergoing CHD interventions. The in-hospital mortality rates for these patients were 27.76% (trisomy 13) and 13% (trisomy 18), ten times higher than what is "expected" for these types of lesions. Median survival, if they survived to hospital discharge, however, was 14.8 years (trisomy 13) and 16.2 years (trisomy 18) for those patients they were able to track. Patients who were identified as having mosaic or partial forms of trisomy 13 or 18 had approximately 2 years longer median survival than patients who were not reported to be mosaic or partial. Causes of death included cardiac (43.5%), respiratory (26.1%) and pulmonary hypertension (13%). The authors conclude that those patients who were selected for cardiac surgery had longer survival than what was previously reported. They argued that their data could be useful when counseling families and deciding whether to offer cardiac interventions to select patients [38].

As these survival data are emerging, disagreement continues among clinicians about what interventions are appropriate to offer. Kaulfus et al. surveyed 378 clinicians from multiple specialties regarding their attitude towards congenital heart surgery for infants with trisomy 18. Survey respondents included genetic counselors, prenatal physicians, and postnatal physicians. In their study only 48% of respondents agreed that discussing the option of cardiac surgery for these patients was appropriate, however 81% agreed that cardiac surgery may offer the benefit of extending the infant's life. Fifty-one percent thought that CHD surgery could improve the quality of life. Some respondents wrote in the comments section that not having access to a cardiac surgeon who was willing to perform the surgery was a reason why they did not bring surgery up as an option. In summary, they concluded: "Ethical concerns and insufficient outcome data were the most agreed upon reasons for not offering cardiac surgery. Trisomy 18 not being uniformly lethal and expressed parental wishes were the most agreed upon justifications for offering surgery." All 6 surgeons surveyed, however, reported performing surgery or being willing to perform surgery for these patients for certain heart lesions [17].

Although the examples of trisomy 13 and 18 are used here, there are many other extracardiac or genetic diseases where the decision to depart from the usual course of CHD treatment or repair may arise: extreme prematurity, congenital diaphragmatic hernia, intractable seizure disorders, other genetic anomalies or syndromes with significant neurodevelopmental delays, and syndromes that affect multiple organs systems and potentially require other invasive procedures. Indeed, this is not a comprehensive list but is intended to provide some examples that pediatric cardiologists and cardiac surgeons routinely encounter. All may lead to disagreements about what is in the best interest of the child and who is permitted to ultimately decide upon the course of treatment.

5 Clinician Perspective

Sometimes pediatric cardiologists and/or cardiac surgeons refuse to offer surgical interventions despite parental requests. In these cases, it is important to understand the reason for placing limitations on parental choice. First, a physician may find that the intervention that is requested will not have the intended outcome or may be technically impossible. For example, a parent may request that a surgeon perform a full repair on an extremely premature infant with Tetralogy of Fallot, pulmonary atresia and multiple aortopulmonary collateral. However, the surgeon may refuse until the infant is larger due to technical reasons or because the surgery is unlikely to be successful based on the infant's weight. Second, a physician may refuse a procedure because he/she does not think the risks are worth the benefits. For example, a surgeon may decline to repair a coarctation of the aorta in an infant who is septic from necrotizing enterocolitis and not expected to live. Another example is a child with trisomy 18 who has hypoplastic left heart syndrome and is not be expected to survive the usual first surgery performed on cardiopulmonary bypass. Here a surgeon may decide to decline to perform the Norwood operation, but may consider a less invasive hybrid procedure (stenting of the patent ductus arteriosus and pulmonary artery banding) in order to allow the child to leave the hospital and go home with family. This example is in contrast to a child with trisomy 18 and a ventricular septal defect where surgical closure is now increasingly offered. These types of refusals are deemed ethically appropriate because the proposed treatment will either not achieve the intended goal, or the risks are considered to outweigh the potential benefits.

Although many use the word "futile" when deciding not to offer medical or surgical interventions, the use of this word can be problematic "because doing so is disrespectful to patients and families, overly empowers clinicians, and stifles communication" [39, 40]. The American Thoracic Society in its policy statement states: "the term 'potentially inappropriate' should be used, rather than 'futile,' to describe treatments that have at least some chance of accomplishing the effect sought by the patient, but clinicians believe that competing ethical considerations justify not providing them… The term 'futile' should only be used in the rare circumstance that an intervention simply cannot accomplish the intended physiologic goal. Clinicians should not provide futile interventions and should carefully explain the rationale for the refusal" [41].

In reality, situations with intractable disagreement remain complex when families want continued medical care despite nuanced explanations and discussions as illustrated by multiple ethical analysis and case reports of CHD and associated anomalies [42–44]. Ultimately, as stated by Lantos, "the fundamental question in debates about futility is whether the doctors' way of understanding what is going on is ultimately so obviously and inarguably correct that it should prevail or whether, instead, the alternative understandings of patients and families are also worthy of consideration" [45].

6 Parental Perspectives

There are few studies that have looked at parental perspectives during real-time decision making about CHD surgery or retrospectively after surgery has occurred. One small survey study of parents whose children had trisomy 18 and had medical or surgical treatment for CHD showed "all respondents agreed that they would choose the same treatment option again, that their child's quality of life was improved by their choice of care, and that the parental experience was enhanced" [46]. Parental satisfaction with the experience was the same in the intervention and medical management group and did not vary based on whether their child was still alive at the time of the survey. Janvier et al. showed that parents of children living with trisomy 13 and 18 describe their children as happy and enriching to the family [21]. Though these studies are small, they point to the ethical dangers of making assumptions about quality of life on behalf of patients without parental input. In the modern era, there are multiple support groups and internet sites where families share stories of their children with trisomy 13 and 18 and the added value these children bring to their family. Parents post about how their children teach them the meaning of unconditional love. Others describe becoming closer to God through the process of caring for their child [47, 48].

7 Societal Burdens

Some may argue that offering cardiac surgery to patients with other severe comorbidities is unethical because it is a poor use of societal resources [19]. Furlong-Dillard et al. used the PHIS database between 2004 and 2014 and identified patients who had CHD surgery and a genetic condition. They found that 15% of patients undergoing CHD (14,714 patients) had an associated genetic condition. They stratified based on surgical complexity and grouped genetic conditions and found that all patients with a genetic anomaly had a significantly longer length of hospital stay and higher total cost than the controls except for the trisomy 21 group [49]. The cost is higher for almost all genetic conditions, even the ones with milder cognitive delays such as 22q11 or Turner Syndrome. Realistically, if cost is the argument for limiting interventions, it will be difficult to decide where to draw the line between different genetic anomalies.

Certainly, other countries with national health systems or reduced resources may set limits of care based on established policy on how resources are deployed to deliver healthcare based on the principle of justice. Resources do need to be adequately utilized in order to maximize good. However, in the United States, the health care model does not currently have broad policy or recommendations on limitations of care. If restrictions on medical or surgical care are going to be made based on expected survival benefit, these decisions need to be made at the governmental policy level. Physicians and clinicians caring for these children should not

be rationing or changing care based on their own assessments of the financial burdens and potential quality of life of the child. Limiting care at the bedside based on quality of life or perceived better allocation of resources may also lead to discrimination against certain populations and lead to further disparities in care.

8 Data Transparency

Over the last decade, there has been a move towards increased transparency and reporting of surgical outcomes in the field of pediatric cardiology and cardiac surgery to improve patient outcomes and health care delivery through knowledge sharing [50]. Lihn et al. in describing their work through the National Pediatric Cardiology Quality Improvement Collaborative, state that "barriers to full transparency persist, including health care organization concerns about potential negative effects of disclosure on reputation and finances, and lack of reliable definitions, data, and reporting standards for fair comparisons of centers" [51]. While we support the move towards increased transparency as part of improving the informed consent process and patient care, how to take into account higher-risk patients becomes imperative. Heart center administrators, pediatric cardiologists, and surgeons who perform CHD surgery may be reluctant to take on patients with multiple co-morbidities including extracardiac or genetic anomalies due to the higher risk profile of these patients and potential inherent increased mortality. This bias may not be overt and occur subconsciously but still results in declining to perform an operation. While pursuing transparency, we must still guard against creating a system where there is inappropriate discrimination against patients with CHD and extracardiac or genetic anomalies.

9 Importance of Shared Decision-Making

When care is complex and prognostication is difficult, the practice of shared decision-making between parents, patients, and clinicians becomes especially imperative. Providing the most accurate and current data is a first step in this informed consent process. Therefore, further research on the long-term morbidity and mortality of these populations is necessary. The research also needs to evaluate the mosaic or less severe genetic subtypes separately since they have been shown to have a better outcome as well [38].

As more surgeons perform cardiac surgery on patients with extracardiac and genetic anomalies in the future, studies will be needed to better assess factors that may influence the likelihood of increased morbidity so that families can be appropriately counseled. For example, preoperative mechanical ventilation in the trisomy 13 and 18 population was shown to be associated with higher mortality despite congenital heart surgery [52]. Delayed intervention and complete repair instead of

palliation may also be better than palliative procedures at prolonging life [38]. Identifying other factors that may predispose to higher morbidity and mortality such as history of previous surgeries, other organ dysfunction and low birth weight are essential to the counseling and shared decision-making that needs to occur on an individualized basis. A comprehensive team-approach should occur with the family to provide balanced and consistent counseling and to avoid potential misunderstanding and mistrust [21].

Finally, data also need to reflect the quality of life of these patients from the parents' perspectives. Relying on physicians' quality of life assessment can be ethically problematic as physicians tend to rate the quality of life for a disabled child lower than their parents rate it [53, 54]. Extreme caution must be taken if the reason to refuse a cardiac intervention is the perception of a poor quality of life of the patient. The conversation with the family instead should be about the risks and benefits of the desired CHD. Is the surgery likely to extend the patient's life in a significant way or is the child so impaired that he/she is likely to have a shortened lifespan regardless of any cardiac intervention?

Sometimes, despite providing as much granular information as possible, parents and physicians might still disagree about whether to pursue cardiac surgery [55, 56]. For diagnoses that are uncertain and complex, the subjective nature of the of the best interest standard can make decision-making challenging. An ethics consultation may be helpful as well as guidelines such as "Non-initiation or withdrawal of intensive care for high-risk newborns" and "Guidance on Forgoing Life Sustaining Medical Treatment" [29, 30]. While allowing for parental discretion and leeway when complexity is high, all available pediatric ethical principles and guiding frameworks may need to be employed to reach a resolution [57–59].

10 Conclusion

A large number of CHD patients will have genetic or extracardiac anomalies. It is important for cardiologists and cardiac surgeons to treat each case and family as unique. Not all patients with the same diagnosis will necessarily end up with the same treatment (or nontreatment) because parental decision-making is crucial. Just as we allow parents to make decisions for their children without such extracardiac anomalies, we must allow parents to make decisions for their children with these anomalies. Parental authority for decisions should only be limited in the rare case where the parental request is out of line with the standard of care for treatment. Importantly, however, as seen from the historical perspective of trisomy 21, the standard of care shifts with time as new surgical techniques improve outcomes and research changes earlier prognoses about some genetic conditions and anomalies. It is imperative, therefore, that cardiologists and cardiac surgeons stay abreast of the developments for conditions that have previously been considered to have an insurmountable risk of high mortality or morbidity.

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