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COMMENTARY

Ethical considerations for cardiac surgical interventions in children with trisomy 13 and trisomy 18

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Abstract

Medical and surgical approaches to children with trisomy 13 and 18 are evolving, and an increasing number of patients are being considered for simple and complex cardiac procedures. This review describes how the shifts in medical and social considerations for children with trisomy 13 and 18 mirror the shifts that occurred 50 years ago for children with trisomy 21. Yet the variability in cardiac lesions, and variability in non-cardiac comorbidities, is much greater for patients with trisomy 13 and 18 than for those with trisomy 21. That variability, combined with the severe neurologic impairment in survivors, complicates the current risk: benefit balance of surgical intervention. Consistent approaches to care for these patients should be built on an evidence base, and should include contributions from specialists in medical ethics and palliative care.

The fields of pediatric genetics, cardiology and cardiac surgery have changed and grown immensely in the last 50 years and continue to do so. As more syndromes, diseases, interventions and procedures are discovered, there are ongoing and new ethical considerations to be debated and discussed (Bittles & Glasson, 2007). Trisomy 21, 13, and 18 are the most common trisomy syndromes associated with live birth: Trisomy 13 and 18 are, respectively, the second and third most common trisomy syndromes behind trisomy 21(Carey, 2010). In the last 50 years we have seen the management for patients with trisomy 21 change dramatically, shifting from a presumption of no surgical intervention to a presumption of surgical intervention (Bittles & Glasson, 2007; Champagne, Lewis, & Gilchrist, 2014). While this is partly because medical and developmental care for patients with trisomy 21 have improved outcomes for these patients, it is also because of increased social and ethical "worth" attributed to the physical, cognitive, behavioral, and relational states typical of patients with this condition (Champagne et al., 2014).

These medical, social, and ethical transitions have more recently characterized deliberations about cardiac surgery for patients with trisomy 13 and 18 (Janvier, Okah, Farlow, & Lantos, 2011; Nelson, Hexem, & Feudtner, 2012). The comorbidities and surgical lesions are less consistent in patients with the diagnosis of trisomy 13 and 18, compared with children with trisomy 21, which undermines evidence-based surgical planning for these patients (Janvier, Farlow, & Barrington, 2016a). During this transitional period, when surgical interventions for infants with Trisomy 13 and 18 are being performed in some settings but not others, it is important to advance dialogue about what is "right" for these patients.

Ethical deliberation about the benefits and burdens of pediatric medical therapies must focus primarily on the child, yet also account for the impact on the child's family given their essential role in the child's quality of life. Some medical therapies, eg antibiotics for meningitis, are considered ethically obligatory, regardless of parent requests, due to their substantial benefit, and minimal harm, for a child. Other therapies, e.g., attempting ECMO for premature infants, are ethically unacceptable, regardless of parent requests, due to their substantial harm, and minimal benefit, for a child. But in between these thresholds of ethically obligatory and ethically unacceptable therapies lies a gray area where treatments result in both benefits and burdens to a child (Murray, Esserman, & Mercurio, 2016). Decisions about such therapies often rely on subjective views about a child's quality of life. And where judgments about quality of life differ between families and clinicians, the family's perspectives are often prioritized, given their special and enduring role with the child (Friedman Ross, 2002).

The combined prevalence of trisomy 13 and 18 including fetal terminations, still births and live births is approximately one in 1800 (Irving, Richmond, Wren, Longster, & Embleton, 2011). The spectrum of medical complexity for each of these genetic syndromes is broad, with up to 39 possible common congenital anomalies associated with each; while these syndromes manifest with variable anomalies,

significant intellectual disability characterizes all survivors (Pont et al., 2006). Some of the more common congenital abnormalities include major congenital heart disease, abdominal wall defects, orofacial anomalies, and central nervous system abnormalities (Pont et al., 2006). Of infants with trisomy 13 and 18, congenital heart disease is present in approximately 38 and 45%, respectively (Pont et al., 2006). Data from the 1960s cites survival of 7–10 days for trisomy 13 and 10–14.5 days for trisomy 18, with no data on patients surviving more than 1 year (Conen & Erkman, 1966; Irving et al., 2011; Nelson, Rosella, Mahant, & Guttmann, 2016; Rasmussen, Wong, Yang, May, & Friedman, 2003). Now 50 years later there are reports that 12–19% of patients with trisomy 13 or 18 survive beyond the first year of life (Irving et al., 2011; Nelson et al., 2016; Rasmussen et al., 2003), with 10–12% of the original population surviving at 10 years of life (Nelson et al., 2016), and some case reports of patients living to the late teenage years (Redheendran, Neu, & Bannerman, 1981). While the majority of children with trisomy 13 and 18 still die in the neonatal period, it is becoming clear that the risk of death decreases after 3–6 months of life and again after 1 year of life (Meyer et al., 2016; Nelson et al., 2016; Nembhard, Kim Waller, Sever, & Canfield, 2001).

Central apnea is a common cause of early death in both trisomy 13 and 18 (Irving et al., 2011; Nelson et al., 2012; Pont et al., 2006). Along with reports of increasing survival over the last 20 years are reports detailing increasing life-sustaining medical interventions for these patients (Nelson et al., 2012). The initial approach in the mid-1900s to the diagnosis of trisomy 13 or 18 as "incompatible with life" may have in part been a self-fulfilling prophecy. Whereas prior to the 1990s resuscitation would not be performed for infants with confirmed trisomy 13 and 18, over the last three decades more and more physicians are resuscitating these neonates (McGraw & Perlman, 2008). In a 2007 survey of neonatologists, 44% would initiate resuscitation on a full term infant with confirmed trisomy 18 and confirmed cardiac disease (McGraw & Perlman, 2008). A review from 1994 to 2009 found that infants with trisomy 13 and 18 diagnosed prenatally were much more likely to forego intensive care, as opposed to infants diagnosed shortly after birth (Boghossian et al., 2014). A review of hospital care for patients with Trisomy 13 and 18 from 1997 to 2009 by Nelson et al. found that a significant number of these patients were undergoing tracheostomy (2–5%), orthopedic procedures (5%) and cardiac procedures (4–7%), with one third of these patients living longer than 1 year of age (Nelson et al., 2012). This review by Nelson et al highlights that this population is living longer and undergoing more invasive procedures (Nelson et al., 2012).

The debates about whether to provide cardiac interventions for infants with trisomy 13 and 18 have multiple parallels to debates the 1970–1980s regarding patients with trisomy 21 (Bull, Rigby, & Shinebourne, 1984; Champagne et al., 2014). At that time, the rights and values of patients with trisomy 21 were evolving simultaneously with the field of pediatric cardiac surgery (Bittles & Glasson, 2007). In the 1940s life expectancy for a patient with trisomy 21 was only 12 years (CDC, 2018), this increased to 25 years in the 1970s and again rose to 49 years the late 1990s (Yang, Rasmussen, & Friedman, 2002) and is currently around 60 years of life (Bittles & Glasson, 2007). The life expectancy for patients with trisomy 21 changed over time, both due to improved living conditions as infants began to live in family homes instead of institutions, and with standard medical treatment and eventually therapeutic procedures and cardiac interventions. Prior to the 1950s the general recommendations from the medical community for babies with trisomy 21 was for them to be placed indefinitely in institutions ("National Association for Down Syndrome," 2018). These institutions had questionable living conditions and infants would receive sub-par medical care ("Global Down Syndrome Foundation," 2018). Choices against medical interventions that might increase quality or quantity of life for these patients were largely based on society's values of cognitive abilities; the intellectual disabilities associated with trisomy 21 altered the value placed on their "personhood," regardless of parent preferences for their care ("National Association for Down Syndrome," 2018). More families started taking their babies with trisomy 21 home in the 1950s and advocating for equal treatment ("National Association for Down Syndrome," 2018). A study in the 1970s showed that children with trisomy 21 raised at home had IQ's 20–30 points higher than children with trisomy 21 raised in an institution (Bennett & Sells, 1979). By the 1980's, patients with trisomy 21 had standard medical care, interventions and cardiac surgeries as to those without trisomy 21 in the 1980s (Champagne et al., 2014).

Almost half of patients with trisomy 21 have congenital heart disease (Freeman et al., 1998). In the 1970s, ethical debates regarding cardiac surgery for children with trisomy 21 (Champagne et al., 2014) were very similar to current debates regarding patients with trisomy 13 and 18. For patients with Trisomy 21, there was initial concern that the risk of mortality during cardiac surgery was much higher than for the general population, thereby indicating that these interventions would not be in the child's best interest (Feingold, 1978). But ongoing research made it clear that the excess mortality was largely due to these patients undergoing surgery much later, with more advanced heart and lung disease from delayed correction, then occurred among the general population (Feingold, 1978). This was also a time when emerging cardiac interventions had elevated risks of morbidity and mortality. During the historical period when outcomes from newly emerging complex cardiac surgery were suboptimal, it was deemed ethical to withhold surgery for certain lesions in any patient, whether that patient had no other co-morbidities or had trisomy 21 (Bull et al., 1984). But as the field of cardiac surgery evolved and the morbidity and mortality rates decreased, the ethical permissibility of not offering surgery to patients with and without trisomy 21 was questioned (Bull et al., 1984). Today, it would be unethical for medical teams to not evaluate candidacy for cardiac surgery for patients with trisomy 21 as the outcomes have become so much better for all patients.

A similar medical and surgical pathway has been evolving for patients with trisomy 13 and 18 over the last 20 years(Nelson et al., 2016). While some of the increasing survival of liveborn infants with these conditions reflect increasing prenatal diagnosis and elective termination of more severely affected fetuses (Meyer et al., 2016), there are studies reporting survival after postnatal cardiac interventions (Kaneko et al., 2008). The spectrum of cardiac disease seen in patients

with trisomy 13 and 18 is broad, with the most common being ventricular septal defects, atrial septal defects, and tetralogy of Fallot (Pont et al., 2006). The wide spectrum of co-morbidities also associated with these conditions means that a set rule for cardiac surgical candidacy cannot be made. Trends over the past few decade suggest that lower-risk cardiac surgeries will be performed on a growing number of infants with trisomy 13 and 18, particularly those who survive the first days of life without the need for intensive care (Nelson et al., 2012). Emerging questions involve whether to engage in higher-risk treatments for these infants, whether that be high-risk cardiac surgeries or low- to moderate-risk surgeries in infants with multiple underlying complications. Recent analysis of The Society of Thoracic Surgeons Congenital Heart Surgery Database demonstrates that surgical complications are so substantial in infants with trisomy 13 or 18 who require preoperative mechanical ventilation (Cooper, Ferguson, Bodurtha, & Smith, 2014) that the authors suggest that this group of infants be considered ineligible for surgery. The data also suggest that high-risk surgeries have excess morbidity and mortality for this population compared with children without trisomy 13 or18 (Cooper et al., 2014).

For any child, it is important to consider whether the burdens related to a high-risk treatment, such as multi-staged single ventricle repair, are so high that it is ethically acceptable to opt for palliative care alone. These considerations should receive even greater emphasis in children with serious underlying genetic conditions. Single ventricle repair is currently offered to patients with trisomy 21 (Peterson et al., 2019). Data from the Pediatric Cardiac Care Consortium suggest that 10 year survival from single ventricle palliation is 67% for children with trisomy 21, compared with survival of 92% in children with no genetic syndrome (Peterson et al., 2019). While these excess risks clearly need to be weighed, the fact that such a large proportion of patients with trisomy 21 will have long-term survival after this procedure suggests that it is reasonable to consider this treatment, pending acceptability of co-morbidities such as lung disease and pulmonary hypertension. For patients with trisomy 13 and 18, there are scant data regarding short-term or long-term survival or other outcomes from complex surgeries, often in the form of case reports (Kukora et al., 2019; Oka et al., 2016). Survival, of course, is not the only outcome that matters—quality of life is also essential. Complex cardiac surgery may be reasonable in a patient with trisomy 21 who has at least moderate potential for self-care, relationships, and communication. Neurodevelopment for patients with trisomy 13 and18 is often severely limited, with life-long dependence on others and minimal communication (Bruns, 2015; Redheendran et al., 1981). The burden of complex cardiac surgery may be even higher for these patients, compared with the benefits that the child is likely to experience. Determining what benefit a complex surgery would be to an infant with trisomy 13 or 18 is difficult because the range of possible co-morbidities is so great, there is great uncertainty for their life-expectancy and how much suffering a parent is willing to put their child through for a certain degree of quality of life also varies between families.

The increasing discussion of medical interventions for infants with trisomy 13, 18, and 21 in social media and other patient-facing forums means that more and more parents may be requesting therapies that are offered at a few centers for these patients (Arthur & Gupta, 2017; Janvier, Farlow, & Barrington, 2016b; Janvier et al., 2019). Most children with trisomy 21, 13, and 18 receive medical care at academic medical centers with the full scope of interdisciplinary services. The team caring for an individual infant with trisomy 13, e.g., may involve maternal-fetal medicine specialists, perinatal hospice providers, general pediatricians, geneticists, general surgeons, pulmonologists, neurologists, and others from the neonatal and pediatric intensive care units. Choices about surgical intervention are made in the context of these large teams. Yet large clinical teams can impede quality communication between various clinicians, and between the clinicians and family. When surgical decisions involve ethical complexity, individual members of these clinical teams may have conflicting values related to life-sustaining interventions for patients with trisomies (Shapiro, Donohue, Kudchadkar, Hutton, & Boss, 2017). Strategies to explore and achieve management consensus are important, including consultation with clinical ethics consultants and palliative care consultants. Several studies underscore the potential for clinician bias to impact patient care; clinician teams should consider evidence-based, consistent protocols to standardize clinical decision-making about these patients from the moment that they present for care (Arthur & Gupta, 2017; Thorvilson & Copeland, 2018). The study of Kaempf et al., regarding treatment decisions for extremely premature infants, suggest that clinical protocols for ethically complex medical care can and do make prenatal and postnatal care more medically and ethically consistent (Dirksen, Kaempf, Tomlinson, & Schmidt, 2017).

Once clinicians have reached agreement about which surgical interventions are reasonable to offer a child with trisomy 13 or 18, clinicians must then help families weigh the different options. Data from parents of children with trisomy 13 and 18 reveal that trust in their infant's clinician is essential (Janvier et al., 2019). This trust and collaboration can be built through open discussion of the child's medical needs and of the family's goals and values for their child (Feudtner, 2007). While one family may not feel that their child's life is worth living if the child will not be able to interact with others, another family may prioritize length of life above all other considerations. High quality communication can help clinicians understand the family well enough that they can offer treatment recommendations based on family values (Feudtner, 2007). It is important to note that shared decision-making does not mean offering parents options and then asking them to make the decision; it means figuring out what kind of assistance parents would like with the decision and then offering that assistance (Feudtner, 2007). A recent study suggested that as many as half of parents of children with trisomy 13 and 18 do not want to be a part of life and death decisions for their child. (Janvier et al., 2019). It is then incumbent upon the medical team to make informed, compassionate recommendations (Feudtner, 2007; Jacobsen, Blinderman, Alexander Cole, & Jackson, 2018). The American Academy of Pediatrics has recommended that palliative care be part of the interdisciplinary team from the time of diagnosis for children with life-threatening

or life-shortening illnesses (Feudtner, Friebert, & Jewell, 2013). The palliative medicine and hospice teams can support clinicians in communication with family and also facilitate longitudinal evaluation of parents' values and goals over the course of a child's hospitalization (Feudtner et al., 2013).

The ethical complexities of cardiac management for children with trisomies will continue to evolve. Substantial shifts in the approach to their care may occur during a clinician's career; it is essential for clinicians to know the current data about mortality, morbidity, and quality of life outcomes for these children and their families. Shifts in care for children with trisomy 21 came at a time when the sharing of medical information was reliant on textbooks, printed journals, and annual meetings. The exchange of information about children with trisomy 13 and 18 can occur much more quickly via registries, online publications, and parent testimonies. Harnessing this information should be the first step in approaching surgical decisions for these patients.

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