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REVIEW

Ethical and practical dilemmas in cardiac transplantation in infants: a literature review

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Abstract

The waiting time in infants for a cardiac transplant remains high, due to the scarcity of donors. Consequently, waiting list morbidity and mortality are higher than those in other age groups. Therefore, the decision to list a small infant for cardiac transplantation is seen as an ethical dilemma by most physicians. This review aims to describe outcomes, limitations, and ethical considerations in infant heart transplantation. We used Medline and Embase as data sources. We searched for publications on infant (< 1 year) heart transplantation, bridge-to-transplant and long-term outcomes, and waiting list characteristics from January 2009 to March 2021. Outcome after cardiac transplant in infants is better than that in older children (1-year survival 88%), and complications are less frequent (25% CAV, 10% PTLD). The bridge-to-transplant period in infants is associated with increased mortality (32%) and decreased transplantation rate (43%). This is mainly due to MCS complications or the limited MCS options (with 51% mortality in infancy). Outcomes are worse for infants with CHD or in need of ECMO-support.

Conclusion: Infants listed for cardiac transplantation have a high morbidity and mortality, especially in the period between diagnosis and transplantation. For those who receive cardiac transplant, the outlook is encouraging. Unfortunately, despite growing experience in VAD, mortality in children < 10 kg and children with CHD remains high. After transplantation, patients carry a psychological burden and there is a probability of re-transplantation later in life, with decreased outcomes compared to primary transplantation. These considerations are seen as an important ethical dilemma in many centers, when considering cardiac transplantation in infants (< 1 year).

What is Known:

- *For infants, waitlist mortality remains high. In the pediatric population, MCS reduces the waiting list mortality.*

What is New:

- *Outcomes after infant cardiac transplantation are better than other age groups; however, MCS options remain limited, with persistently high waiting list mortality.*
- *Future developments in MCS and alternative options to reduce waiting list mortality such as ABO-incompatible transplantation and pulmonary artery banding are encouraging and will improve ethical decision-making when an infant is in need of a cardiac transplant.*

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Keywords Heart transplant · Cardiac transplant · Waiting list · Infants

Background

In a significant number of children with end-stage heart failure, when medical treatment becomes insufficient, advanced treatment options such as mechanical cardiac support (MCS) or heart transplantation are needed. For example, Oster et al. described children with a univentricular heart to have a transplant-free survival of only 58–85% directly after palliation surgery, decreasing to 52–72% 20 years after palliation [1]. Depending on the age of the patient, indications for heart transplant differ. Most infant patients listed for heart transplantation have congenital heart disease (CHD) as indication, whereas in adolescent patients, intrinsic cardiomyopathies are the most common cause for transplantation [2].

A major problem worldwide is the considerable morbidity and mortality during the waiting time for heart transplantation, as waiting times are usually long due to a scarcity of donors, especially for infants [3]. In Europe, the scarcity is even more acute. Numbers show that there is a significantly higher donor age and a larger donor-recipient weight mismatch in pediatric heart transplantation compared to North America [4–6]. This is reflected in the Eurotransplant results, where the infant population comprises approximately 29% of the patients on the transplant waiting list but only 19% of actual heart transplantations performed [7].

Of the annual 150 infant cardiac transplants performed worldwide, approximately 7 are performed in Eurotransplant, which is more than ten times less than the reported American numbers, with a significantly higher number of transplants performed in small- or medium-volume centers and less CHD patients compared to the Northern American colleagues [4, 7–10].

With less patients and less experience, the success rate decreases. Therefore, it should be taken into consideration that in Europe, there is a higher probability of treatment taking place in a center with limited experience in infant cardiac transplantation and bridge-to-transplant options, possibly resulting in even higher morbidity and mortality [9, 10].

Consequently, the decision whether to list an infant for cardiac transplantation still remains a dilemma for pediatric cardiologists and cardiac surgeons in Europe. In this article, we aim to describe outcomes, problems, and considerations in cardiac transplantation in infants to facilitate decision-making.

Methods

We used Medline (accessed by Pubmed) and Embase as data sources. Initial search was from January 2009 to June 2020. In order to obtain the most relevant articles, we filtered for subjects under 1 year of age, which defined our population. As comparative population, we also analyzed articles concerning other pediatric age groups. References listed in selected articles were manually scanned for relevant study population and outcome parameters with publication date up to March 2021.

A variety of search terms were used, to increase sensitivity and obtain information regarding all different aspects associated with the intervention reviewed in our age group. The most frequently used were “infant” and “neonate” in combination with “heart transplantation” or “cardiac transplantation”. To include specific aspects, additional search terms were used such as “waiting list”, “mechanical cardiac support”, and “ventricle assist device”. A specific search for European patient populations was made.

Only full-text articles with the original text written in English were included. Articles concerning a study population that was not similar to our patient population, such as studies with a limited number of infant patients, were excluded. Articles with an overlap in results were also excluded.

Results

Heart transplantation in infancy

Waiting list outcomes

As previously mentioned, the waiting time for heart transplantation is usually prolonged in the infant population due to the scarcity of donors.

Eurotransplant numbers show that of all infants that were registered for transplantation, 43% received a heart transplant, compared to 53% of all children aged 1–10 years and 65% of all children aged 11–15 years. Notably, in the infant population, 12% were delisted because of clinical improvement, compared to 6% in children from 1 to 10 years and 10% in children from 11 to 15 years [7].

Therefore, the mortality risk while waiting for a suitable organ is an important consideration. Reinhardt reported a 17% mortality of all children during the first 6 months on the transplant list in the UK [8]. The waiting list mortality in infants and children < 10 kg is significantly higher than that in children older than 12 months, with an even greater risk at < 3 kg [9, 11, 12]. Of the infants listed, 32% died in the first year without receiving a transplant, compared to 20% in children of 1–10 years and 15% for children of 11–15 years [7]. Similar numbers were reported in Canadian and American populations with a mortality over 25%, approximately 4 times more than for other age groups [9, 12–15].

The higher mortality in infants might in part be explained by the high percentage of infants being listed as a result of CHD (75% compared to 25% in older age groups), with significantly higher mortality rate (61% in congenital heart disease, compared to 27% in cardiomyopathy and 18% in myocarditis) [16, 17]. The other reason for a higher mortality is the limited options for bridging to transplantation for infants, most of whom need support to survive to transplantation, more specifically with mechanical cardiac support (MCS) [9].

Survival

With a 1-year survival of 88% and median survival of 20–25 years, primary transplant in infants is more successful than that in older children, where median survival is reported to be 12–17 years [3]. For the neonatal population (0–30 days), John et al. reported an even higher median survival of > 25 years. Re-transplant rate was around 15% with median time to re-transplant being 11.4 years. The higher success rate in neonates and infants is probably due to a less-developed immune system with less risk of rejection [18].

The survival rate of infant heart transplantation is affected, in an important way, by the indication for transplantation. Transplantation for dilated cardiomyopathies has an improved success rate compared to heart transplantation for hypertrophic cardiomyopathies and CHD (approximately 15% higher survival rate and a 3-year longer median survival), probably due to higher perioperative risks and mortality in the second group. After the perioperative period, survival is similar [2, 19].

Complications

In children as well as in adults, heart transplant carries a considerable risk. However, post-transplant complications such as cardiac allograft vasculopathy (CAV), post-transplant lymphoproliferative disease (PTLD), and end-stage renal failure occur less frequently in neonates and infants than in older children[3, 18, 20]. For example, 22% of all children experience rejection in the first year after cardiac transplant and 65% of all patients develop this problem at least once in their lifetime. In contrast, Chinnock et al. reported that only 30% of the infants will experience a rejection episode within 20 years after transplant [3, 18, 20].

The incidence of CAV in infants 10 years after transplant is up to 20% and increases progressively over time to 40% after 25 years, which is lower than that in older age groups [3, 18, 20]. With acute rejection and CAV comprising respectively 10% and 20% of deaths 10 years after transplant, these lower complication rates positively influence the overall survival rate [4]. Seven percent of infants who survive transplantation ultimately need kidney dialysis, compared to 13% in the other pediatric age groups. PTLD occurs in 22% of the infants after 25 years [3, 18, 20].

Life after transplantation

Studies show that the majority of neonates post-transplantation achieve normal height and weight for their age, as well as normal educational degree although cognitive abilities are slightly lower compared to healthy peers. Social interaction is at a normal level [18, 21, 22]. In terms of functional status, 80% of patients describe this as good and with no or minor restrictions in activities [4].

However, frequent hospital visits, medical examinations, and therapies due to post-transplant morbidities pose a significant burden. There are no studies that refer to quality of life (QoL) after infant cardiac transplantation specifically, but QoL has been tested in the pediatric population where infants were included. Although quality of life is higher after pediatric cardiac transplantation than before and physical endurance increases greatly, all pediatric patients and their families report increased fear and anxiety. Thirty-four percent of all (older) patients clearly describe post-traumatic stress symptoms and 22% depressive symptoms, especially in adolescence where it contributes to body image issues. Post-traumatic stress has also been described in parents of heart transplant recipients [19, 21, 23–25]. More than 25% of all transplant patients and their families have emotional adjustment difficulties, with a similar risk for impaired social quality of life as children with residual or palliated heart disease [8].

Mechanical cardiac support

Pediatric population: evolution over time

For patients who are not stable enough after being listed while waiting for transplant, mechanical cardiac support (MCS) might be needed [27, 28].

In adults, the use of ventricle assist devices (VAD) has significantly improved the survival rate on the waiting list with 17% [9]. In the pediatric population, MCS initially did not have similar beneficial outcomes. Lorts et al. reported that 29% of all pediatric patients supported by MCS did not reach a positive end point such as recovery or a successful bridge to transplantation [29]. Outcomes were worse for the subgroup of patients with CHD, with a mortality of 36–53% (compared to 12% in other patients) and a reduced transplant rate of 29% after 6 months compared to 60% in the general population, due to the younger age and sicker patients [19]. However, after a successful heart transplant, the long-term outcomes between patients supported by VAD and the rest of the cohort were comparable [19].

With growing experience, better results were seen in the pediatric population with a reduction of waiting list mortality rate from 26 to 13% in children reported by Zafar et al. [9]. Consequently, the use of MCS has increased with 20–37% in all pediatric patients. European numbers also showed a

reduction in waiting list mortality in children from 25 to 18% [4, 7]. However, EUROMACS reported a transplant rate of only 51% of all children after 24 months on the waiting list with MCS support, which remains lower than the US numbers [30].

Significantly, patients with fewer VAD options, such as patients < 10 kg and children with CHD, had a higher waiting list mortality, regardless of the era they were transplanted in.

MCS in infants

In smaller patients, practical difficulties are commonly related to specific anatomical limitations. The Berlin EXCOR (a paracorporeal pulsatile VAD) is the most popular in smaller patients as it can be implanted in patients with a body surface area (BSA) of 0.6 m^2 or less [31]. Despite its advantages, various major adverse events are observed, such as thrombosis in 50%, infections in 50–70%, bleeding in 40–80%, and neurological complications leading to mortality in 30% [31]. Furthermore, infections, bleeding, heart attacks, mediastinal bleeding, stroke, and mechanical complications occur frequently in smaller children [26].

Additionally, there is an increased reliance on ECMO support in smaller children, with 17% of the patients suffering permanent neurological dysfunction, which results in higher mortality rates and lower transplant rates [26].

Blume et al. reported a 53% mortality rate after 6 months of MCS for infants compared to 20% for children > 11 years [32]. Data published by Conway et al. showed a mortality of 64% in children < 5 kg (compared to 25% mortality in children > 5 kg) and a transplantation rate of 27% for infants supported for bridge to transplant or recovery [33]. Almond et al. reported that 2 out of 3 of the infants < 5 kg supported with the Berlin EXCOR died [34]. For those patients who needed cardiac surgery and/or ECMO prior to a VAD, the mortality rate was unacceptably high at 92% [35].

These outcomes are considerably lower compared to older children supported with VAD, having a mortality of 14% in the VAD only group reported by Dipchand et al. [36]. This difference is due to the fact that the pump volume cannot be sufficiently reduced in smaller children. Another problem in smaller children is that the smaller ventricular cavities can cause obstruction of the inflow cannula [32, 33, 35, 37, 38]. This reflects in the percentage of these infants being bridged to transplant with MCS. ISHLT reported 23% of all infants being bridged with MCS [8].

Outcomes are worse again in CHD patients. In patients with congenital heart disease, Morales et al. reported that no neonates and only 25% of all children aged 1–12 months who were bridged with Berlin EXCOR received a transplant [37]. Rossano et al. report only 12% of infants with CHD being bridged to transplant with MCS, with ECMO used as commonly as VAD, in contrast to 50% of older children with dilated cardiomyopathy that received MCS with only 3% bridged by ECMO [4]. With ECMO intrinsically entailing a higher mortality risk, mortality numbers for CHD patients are considerably worse [4].

Alternative options

An alternative option for bridge to transplant in patients < 15 kg with dilated cardiomyopathy is the application of pulmonary artery banding [20, 26, 39, 40]. In our center, pulmonary artery banding has been successfully used in a number of patients as a bridge-to-transplant or bridge-to-recovery. This technique might be helpful provided that the right ventricular function is preserved. Progressive percutaneous debanding is possible in children showing partial or complete myocardial recovery (if a specific surgical procedure is followed when banding) and is useful in both bridge-to-recovery and bridge-to-transplant.

ABO-incompatible transplant in infants was pioneered in 1996 in Toronto [41]. This technique is advantageous in infancy, before the onset of isohemagglutinin production [42]. Several studies show that there are no significant differences in rejection, complications (CAV, PTLD, and renal dysfunction), survival or re-transplantation rate between ABO-compatible and ABO-incompatible cardiac transplant in infants, even when donor-weight ratio was in excess of 2.5 [3, 41, 43, 44]. Therefore, it can be used as a safe and successful tool to reduce waiting list time and consequently an estimated waiting list mortality reduction of 20–25% [18].

Xeno-transplantation or bio-engineered hearts might be promising techniques in future, but are still only experimental at present [45].

Discussion and ethical considerations

In any medical decision, ethical considerations are important and the following four basic principles need to be considered: beneficence, non-maleficence, autonomy, and justice. To evaluate non-maleficence and beneficence, outcomes of listing for transplantation and transplantation itself are the most significant parameters.

As previously discussed in detail, outcomes are good for those infants who receive a cardiac transplant with 88% 1-year survival after transplant. A survey of pediatric transplant cardiologists in the USA showed that clinicians thought that an acceptable survival rate was 73% at 1 month, 70% at 1 year, and 50% at 10 years. This makes neonatal and infant heart transplantation acceptable, considering transplantation surgery by itself [46].

However, taking into account the substantial waiting list mortality (32% on Eurotransplant) and even higher in infants

with CHD or in need of ECMO, outcomes might not be considered acceptable anymore. Although waiting list mortality has decreased significantly with the use of MCS over time in the pediatric population, the same favorable outcome has not been achieved in smaller children (< 10 kg) with a mortality rate of 51% in EUROMACS or even higher in infants with CHD after cardiac surgery (up to 92%) [47]. For those who can be bridged with MCS, complications remain frequent (25–40% of the infants with VAD) [26]. Permanent injury such as neurological dysfunction is not uncommon, especially in patients in need of ECMO.

Therefore, efforts to decrease waiting list time are welcome and valuable. The number of infant donors has further decreased because of successful sudden infant death syndrome (SIDS) prevention and better car seats [8]. Furthermore, Eurotransplant numbers show that 17% of all donors (< 2 years) are rejected because there is no suitable acceptor on the waiting list [7]. Possible solutions for this allocation problem are transplantation with ABO-incompatible donation, donations after circulatory determination of death, and donation by neonates born with anencephaly, despite inherent ethical dilemmas [2, 9, 18]. Additionally, further experience and advance in bridging options (MCS or alternative) in infants are expected to decrease mortality and complication rates. Careful patient selection when considering MCS or transplantation remains important.

Although the main goal is to increase survival and quality of life, heart transplantation is not curative and this needs to be communicated to parents and care-givers as well as older recipients themselves. In younger patients (at the time of first heart transplantation), the need of re-transplantation later on needs to be considered. Since 15% of the neonatal transplant patients need a re-transplant with a median time to transplant of 11.4 years, re-transplantation will be necessary during adolescence in a significant amount of patients. Compared to primary transplantation, re-transplant is associated with similar short-term survival but increased long-term morbidities, most importantly rejection [16]. However, primary transplantation allows future decision-making by the child itself, which is not possible in infancy.

Furthermore, after primary transplant, patients and their families carry a significant psychological burden with increased anxiety and depressive symptoms after transplantation, which significantly reduces their quality of life. However, primary transplant is reported with a better quality of life and functional status than other palliative options with lower survival rates [1, 4].

Before any decision is made to list an infant for cardiac transplantation, all these arguments should be taken into consideration by physicians and communicated to parents (or guardians), fully informing them of the risks and outcomes associated with pediatric cardiac transplantation, both in the short and long term, physical as well as psychosocial.

Conclusion

In conclusion, outcomes for neonatal and infant heart transplantation are generally satisfactory, but specifically for those who reach transplantation. The main predicament is the scarcity of donors and the limited options for successful bridge-to-transplant options in neonates and infants, which substantially increases waiting list mortality.

In many European centers, ours included, the decreased survival in infants under 1 year of age, in combination with reduced quality of life (both physical and psychological) and the probability of re-transplantation later in life (with poorer outcomes than for primary transplant), can lead to a reluctance in recommending cardiac transplantation. Obviously, joint decision-making with parents is essential after fully explaining all issues related to pediatric and infant heart transplantation in the short and long term.

However, cardiac transplantation in infants under 1 year of age will probably increase in many centers if new bridge-to-transplant options become available, with reduction of morbidity and mortality on the waiting list. Therefore, further research and development of these options is highly encouraged.

Limitations

Recent Eurotransplant numbers (after 2010) are not available and therefore not included in this review. Also, quality of life data are reported in a general pediatric population with infants included. More favorable would be results limited to an infant population.

Abbreviations CAV, Cardiac allograft vasculopathy; CHD, Congenital heart defects; ECMO, Extra-corporal membrane oxygenation; MCS, Mechanical cardiac support; PTLD, Post-transplant lymphoproliferative disease; SIDS, Sudden infant death syndrome; QoL, Quality of life; VAD, Ventricle assist device

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Prof. Dr. Michel De Pauw: contributed to writing the paper
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Dr. Thierry Bové: contributed to writing the paper
Dr. Joseph Panzer: last author: designed the paper, analyzed research, and contributed to writing the paper

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