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Pediatric heart allocation and transplantation in Eurotransplant

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Summary

Pediatric heart allocation in Eurotransplant (ET) has evolved over the past decades to better serve patients and improve utilization. Pediatric heart transplants (HT) account for 6% of the annual transplant volume in ET. Death rates on the pediatric heart transplant waiting list have decreased over the years, from 25% in 1997 to 18% in 2011. Within the first year after listing, 32% of all infants (<12 months), 20% of all children aged 1–10 years, and 15% of all children aged 11–15 years died without having received a heart transplant. Survival after transplantation improved over the years, and in almost a decade, the 1-year survival went from 83% to 89%, and the 3-year rates increased from 81% to 85%. Improved medical management of heart failure patients and the availability of mechanical support for children have significantly improved the prospects for children on the heart transplant waiting list.

Introduction

Pediatric heart transplants (HT) account for 6% of the annual transplant volume in Eurotransplant (ET). In the last decade, each year an average of seven infants (<12 months), 16 children aged between 1 and 10 years, and 14 aged between 11 and 15 years received a HT. The first heart transplantation performed in infants in ET occurred in 1987 [1], while the first child (1–15 years) was transplanted 2 years earlier in 1985 [2]. The longest surviving HT pediatric patient is now into its 26th post-transplant year with the same graft.

Unfortunately, there is a shortage of fitting donor hearts, and many pediatric HT candidates die while waiting for a transplant. In ET, infants and children aged 1–10 years and 11–15 years have a 2.3, 1.5, and 1.2 times higher risk of dying on the waitlist compared with adults [3].

Heart allocation in ET is based on the principles of urgency and equity, where the sickest patients and those with a reduced chance of finding a suitable donor heart are prioritized. Similar to the discussion in the USA on new renal allocation models, equity is likewise conceived as fair inning and prioritizing patients who have had fewer healthy life years [4–6]. The Eurotransplant Thoracic Advisory

Committee (EThAC) has applied this principle in both their heart and lung allocation schemes: by granting a high urgency status to all pediatric heart transplant candidates, and by assigning all children on the lung transplant waiting list and aged <12 years the highest lung allocation score (LAS) value [7].

When is a child a child? The WHO defines the pediatric age between 0 and 18 years (www.WHO.int); however, ET since its start in 1967 has considered and standardized 16 years as the ceiling age for a pediatric status. But a threshold based on age makes no sense if size is the limiting factor in finding a suitable donor; for that reason, the EThAC has abolished the concept of time as defining factor for pediatric status and introduced a definition based on medical grounds, namely delayed bone maturation.

The study aims to give an historical overview of the pediatric heart allocation policies and of the evolution of waitlist and of post-transplant death rates.

Methods

Study population

To analyze the waitlist outflow events, all heart-only transplant candidates, aged <16 years, listed in ET between August 23, 2000 and December 31, 2010 were included (n = 687). All patients were followed up from time of listing until heart transplantation (HT), death on the waiting list, or closure date (December 31, 2011), whichever came first.

Time trends in waiting list size and transplant numbers are given for the period 1997–2012.

Definitions

The current heart allocation policy in ET is ruled by urgency and waiting time since August 23, 2000. Patients with high urgent (HU) status are prioritized over elective patients; within the same urgency level, the patient with the longest waiting time is the first to get the heart offer. In case of pediatric donors (<16 years), pediatric HT candidates (<16 years) are prioritized, but only in the same urgency level, called the pediatric donor-to-recipient match.

General criteria for HU status have been agreed upon by all eight countries in ET (www.eurotransplant.org). Actual assignment of the HU status is performed by a team of three independent transplant experts, who decide by a majority vote—and guided by the HU criteria—whether a patient can be upgraded and/or can remain in his current urgency level. Transplant centers can submit HU requests to ET on any listed candidates.

Until April 23, 2011 (Table 1), HU criteria for pediatric HT candidates were similar to those for adult transplant candidates, except for children <45 kg—who are all considered as HU patients.

Table 1. Overview of pediatric heart allocation policies.

August 23, 2000—Start of the high urgent (HU) heart allocation scheme	
Priority for pediatric donor:recipient pair	Hearts from donors <16 years are first allocated to HTx candidates <16 years within each urgency tier, first high urgent, then urgent, then elective
Pediatric status	HT candidate <16 years at time of organ offer
Pediatric HU status	<45 kg or Admitted to an ICU and CI <2.2 l/min/m^2 and SV02 < 55% and PCWP ≥10 mmHg, while on IV inotropes therapy for at least 48 h; and signs of beginning secondary organ failure or Life threatening complications while on assist device
September 1, 2005- Introduction of the urgent (U) status	
Pediatric U status	Admitted to the hospital and on Continuous IV inotropes therapy or Documented intractable recurrent ventricular rhythm disorders or End-stage transplant vasculopathy or Persistant angina pectoris or Assisted device complications
April 23, 2011—Medical definition of a pediatric status	
Pediatric status	HTx candidate <16 years at time of organ offer or still in maturation proven by X-ray of left hand
Pediatric HU status	HTx candidates with a pediatric status, where the hospitalized children are prioritized. The U status is abolished.
ABO blood group incompatibity	HTx candidates under 2 years, from authorized centers, are selected for the match in case of ABO blood group incompatible heart offers

HT, heart transplants; HU, high urgent.

As of that date, two major changes in the pediatric heart allocation policy were introduced in all ET countries. First, a medical definition of the pediatric status was implemented. In order to be eligible for a pediatric status, patients have to be either under the age of 16 years or they should have a delayed bone maturation in case they are already 16 years of age. Delayed bone maturation is documented with an X-ray of the hand of the transplant candidate. The second change is that all patients with a pediatric status are treated as HU patients in the allocation scheme.

By doing so, all children would jump ahead of the adults in the organ offering process. These new rules were introduced with the following objectives: (i) to avoid the use of pediatric donor hearts for adult candidates and (ii) to prioritize the use of all suitable adult donors for pediatric candidates. To avoid that waiting time would become the only allocation factor among these pediatric candidates, hospitalized children get priority over those waiting at home.

Statistics

The probability of waiting list mortality and the probability of a HT within 1 year after listing were calculated with the competing risk method, thereby accounting for multiple waiting list outcome options [8]. Demographic and clinical variables were ascertained for their association with outcome events and tested using a Wald test.

Post-transplant survival was modeled using Kaplan–Meier method and compared using the log-rank test. Multivariable analyses were performed using Cox proportional hazard regression analysis.

For all analyses, a $P < 0.05$ was considered significant. All statistical analyses were performed using SAS, version 9.1 (SAS, Inc., Cary, NC, USA).

Results

Yearly activities

Of the 9677 HT performed in ET between 1997 and 2012, 588 recipients (6%) were children aged <16 years or aged ≥16 years with a delayed bone maturation. In 2012, 7 (19% of all) pediatric HT were performed in infants (age <12 months), 18 (50%) in children aged 1–10 years, 9 (25%) in children aged 11–15 years, and 2 (6%) HT were performed in children ≥16 years but with a delayed bone maturation (Fig. 1).

During the last 13 years, the pediatric HT WL has increased from nine candidates in 2000 to 39 in December 31, 2012. The major increase occurred in the group of children aged between 1 and 10 years (Fig. 1).

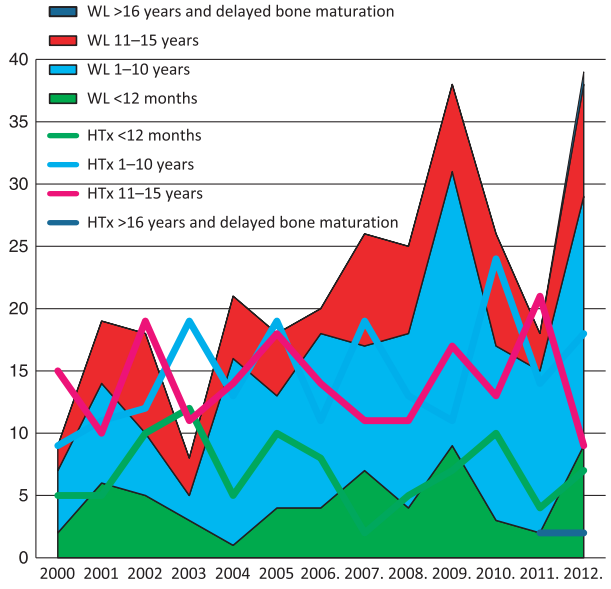

Figure 1 Pediatric heart waiting list and heart transplants in Eurotransplant in period 2000–2012.

The number of patients—stratified by diagnosis—who are registered on the pediatric heart transplant waiting list in the period 1997–2012 is shown in Fig. 2. Patients with DCM and congenital heart diseases constitute the major groups (52% and 26%, respectively in 2012).

Demographic statistics

The characteristics of the study cohort for the waitlist outflow analysis are given in Table 2. Twenty-nine percent of the transplant candidates were infants, while 39% were between 1 and 10 years, and 32% were between 11 and 15 years of age. Waitlist mortality at 1 year was 22% for the whole cohort, while 54% of all patients were transplanted within the first year after listing.

Compared with the transplanted cohort, the patients who died on the waiting list were younger ($P < 0.0001$), more often listed for congenital heart disease ($P < 0.0001$), weighted less ($P < 0.0001$) and were smaller ($P < 0.0001$); they were also small-for-age ($P < 0.0001$), more often in a nontransplantable status (NT; $P < 0.0001$), more often on extra-corporeal membrane oxygenation (ECMO) support ($P = 0.003$) and more often had previous heart surgeries prior to HT listing ($P = 0.025$).

Waitlist outcome

The 1-month, 3-month, and 1-year waitlist mortality for pediatric HT candidates listed between 1997 and 2012 fluctuates between 1.6%, 9.4%, and 12.5% in 2007 and 9.7%, 25.4%, and 30.2% in 2011 (Fig. 3).

Age category-specific waitlist outcomes are shown in Fig. 4a–d. The probability to receive a HT within 1 year for infants listed in ET between 2000 and 2010 was 42.5% vs. 53.0% for children aged 1–10 years and 64.7% for children aged 11–15 years ($P < 0.0001$). Notably, reflecting early referral, 12% of the infants were delisted because of improvement of their condition prior to HT.

Results from the multivariate model on the chance to receive a transplant show that the factors age ($P = 0.036$), primary diagnosis ($P = 0.007$), ABO blood group (0.001), height-for-age ($P = 0.007$), and prior heart surgery ($P = 0.023$) were independent factors in predicting the probability to receive a heart transplant (data not shown).

The risk of dying on the HT waiting list within 1 year was 32.0%, 19.9%, and 15.4% for infants, for children aged 1–10 years, and for children aged 11–15 years, respectively ($P = 0.012$; Fig. 4a–c). In adults, the 1-year waiting list mortality rate was 16.0%.

Multivariate analysis on the risk of dying on the waiting list shows that the factor primary diagnosis and a high serum creatinine level were independent predictors of death before transplantation. Waiting list mortality was higher

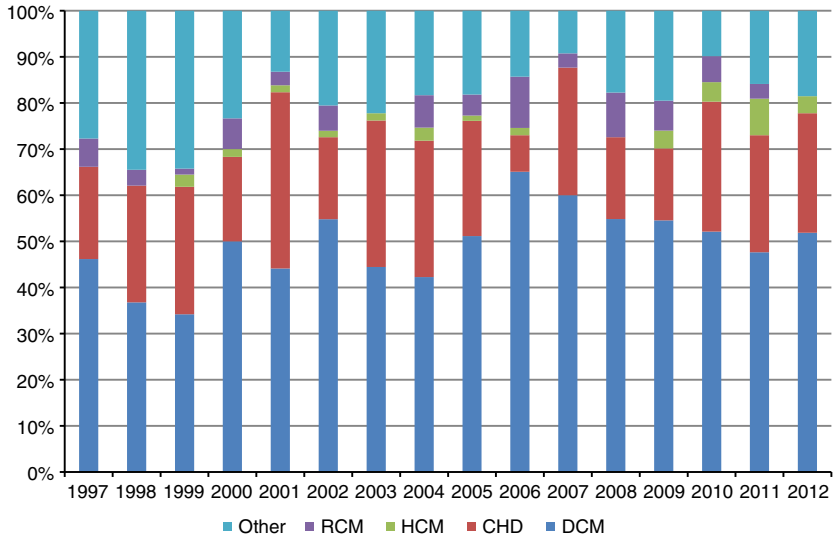

Figure 2 Pediatric heart transplant waiting list, by indication, in Eurotransplant 1997–2012 (at year's end).

for patients with congenital heart diseases or with a hypertrophic cardiomyopathy (HCM). Pretransplant prognosis was different among the cardiomyopathy patients, where an etiology of HCM yielded a hazard ratio of wait list death of 4.89 (95% CI: 1.81–13.18) versus DCM ($P = 0.007$, data not shown). Notably, children on ventricular assist device (VAD) were not more likely to die on the waiting list (WL) compared with children without a VAD ($P = 0.91$; Data not shown).

Post-transplant outcome

The 1- and 6-month and the 1- , 3-, and 10-year survival rates for pediatric transplants performed between 1997 and 2007 are shown in Fig. 5. For the most recent cohorts, the rates are 95% at 1 month, 90% at 6 months, 89% at 1 year, 85% at 3 years, and 64% at 10 years.

In order to study several patient characteristics in detail, the cohort of pediatric patients transplanted between January 1, 2002 and December 31, 2010 ($n = 366$) was analyzed. The 1-year patient survival rates were 88% for infants, 87.7% for children aged 1–10 years, and 84.8% for children aged 11–15 years ($P = 0.64$). In comparison, the 1-year survival rate in adults was 79.5%. Primary diagnosis was a significant predictor of death after transplantation, both in a univariate and multivariate model, wherein patients with DCM had the best outcome ($P = 0.018$; Data not shown).

Heart donor usage and discard rates

In the context of the ET heart donor score study, it was observed that 38.2% of all reported donors were not used for transplantation [9]. For pediatric heart donors, this discard rate was 45.2%; of these, in 8.8%, the heart was not used for transplantation because there was no suitable candidate on the list, in 17.1%, the quality of the heart was insufficient; and in 19.3%, the transplantation did not take place for other reasons (Fig. 6). The absence of transplant candidates at time of donor offer is more stringent for donors under 2 year, where 15% of the available donor hearts were discarded due to the lack of a suitable patient.

Discussion

This study aims at describing the relevant trends in pediatric heart transplantation in ET, from success rates with or without transplantation to the utilization rates of pediatric donor hearts.

Due to improved medical management of patients on the list and the availability of mechanical support for infants and children, death rates on the pediatric heart transplant waiting list in ET have decreased over the years, from 25% in 1997 to 18% in 2011. Within the first year after listing, 32% of all infants (<12 months), 20% of all children aged 1–10 years, and 15% of all children aged 11–15 years have died without having received a heart transplant.

Our data further show that waiting list mortality is higher for patients with congenital heart diseases or with a HCM and for those with a high serum creatinine level. Remarkably, failure to thrive (expressed by the height-for-age *z*-score) [10], mechanical ventilation [11,12], nor mechanical circulatory support in those with reduced left ventricular ejection fraction or impaired ventricular function [13] showed statistical significance in predicting waitlist death. Although the chances for receiving a transplant differ significantly between the blood group ABO

Table 2. Demographic statistics outcome within 1 year for pediatric transplant candidates listed in Eurotransplant between August 23, 2000 and December 31, 2010 [$n = 687$].

	n (%)	HT (%)	Died on WL (%)	*P*-value
Total	687	369 (54)	151 (22)	
Age				
<12 months	200 (29)	85 (23)	64 (42)	<0.0001
1–10 years	266 (39)	141 (38)	53 (35)	
11–15 years	221 (32)	143 (39)	34 (23)	
Diagnosis				
CHD	161 (23)	68 (18)	51 (34)	<0.0001
DCM	363 (53)	223 (60)	54 (36)	
HCM	13 (2)	5 (1)	4 (3)	
RCM	40 (6)	27 (7)	9 (5)	
Other	110 (16)	46 (12)	33 (22)	
ABO blood group				
A	281 (41)	161 (44)	53 (35)	0.18
AB	37 (5)	25 (6)	9 (6)	
B	94 (14)	47 (13)	28 (19)	
O	275 (40)	136 (37)	61 (40)	
Sex (% male)	381 (56)	204 (55)	86 (57)	0.73
Weight (kg)				
<10	233 (34)	105 (28)	73 (48)	<0.0001
10–19	144 (21)	71 (19)	32 (21)	
20–39	165 (24)	94 (25)	28 (19)	
40–59	103 (15)	74 (20)	10 (7)	
≥60	42 (6)	25 (7)	8 (5)	
Height (cm)				
<76	203 (30)	86 (23)	70 (46)	<0.0001
76–100	130	66	26	
101–140	146	77	29	
140–160	112	69	19	
>160	96	71	7	
Height-for-age (*z*-score)				
<−3	111 (16)	41 (11)	38 (25)	<0.0001
−3.01 to −2	78 (11)	36 (10)	27 (18)	
−2.01 to −1	120 (18)	64 (17)	24 (16)	
−1.01 to 1.00	282 (41)	180 (49)	48 (32)	
1.01 to 2	57 (8)	29 (8)	9 (6)	
2.01 to 3	21 (3)	10 (3)	2 (1)	
>3	18 (3)	9 (2)	3 (2)	
VAD (% yes)	62 (9)	35 (9)	15 (10)	0.88
Retransplant (% yes)	24 (3)	12 (3)	6 (4)	0.68
Urgency at delisting				
Elective	199 (29)	98 (27)	47 (31)	<0.0001
HU	379 (55)	271 (73)	65 (43)	
NT	109 (16)	0	39 (26)	
ECMO (% yes)	12 (2)	1 (0.3)	5 (3)	0.003
Mechanical ventilation (% yes)	46 (7)	21 (6)	15 (10)	0.084
IV cathecholamines (% yes)	103 (15)	61 (17)	19 (13)	0.26
Creatinine (mg/dl)	0.53 (0.38–0.80)	0.60 (0.40–0.84)	0.56 (0.36–0.80)	0.73
Bilirubine (mg/dl)	0.80 (0.42–1.20)	0.80 (0.40–1.16)	0.80 (0.50–1.56)	0.39
Previous Heart surgery (% yes)	74 (11)	28 (8)	21 (14)	0.025
ICU stay (% yes)	124 (18)	73 (20)	22 (15)	
Period				
2000–2005	364 (53)	220 (60)	92 (25)	0.67
2006–2010	323 (47)	194 (60)	75 (23)	

CHD, congenital heart disease; DCM, dilated cardiomyopathy; ECMO, extra-corporeal membrane oxygenation; HCM, hypertrophic cardiomyopathy; HT, heart transplants; HU, high urgent; NT, nontransplantable status; RCM, restrictive cardiomyopathy.

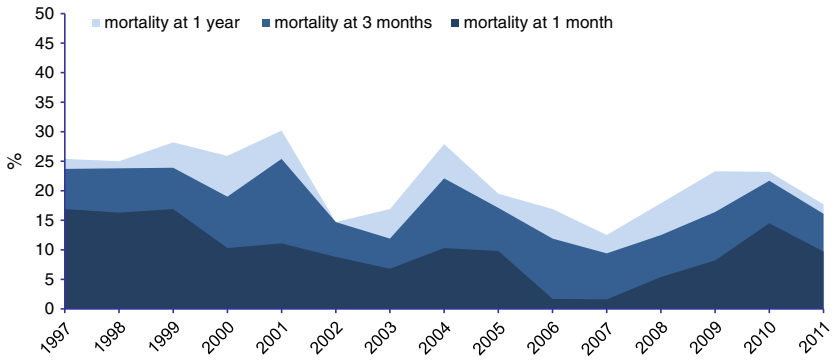

Figure 3 Mortality on the heart transplant waiting list for all pediatric transplant candidates listed in Eurotransplant 1997–2011.

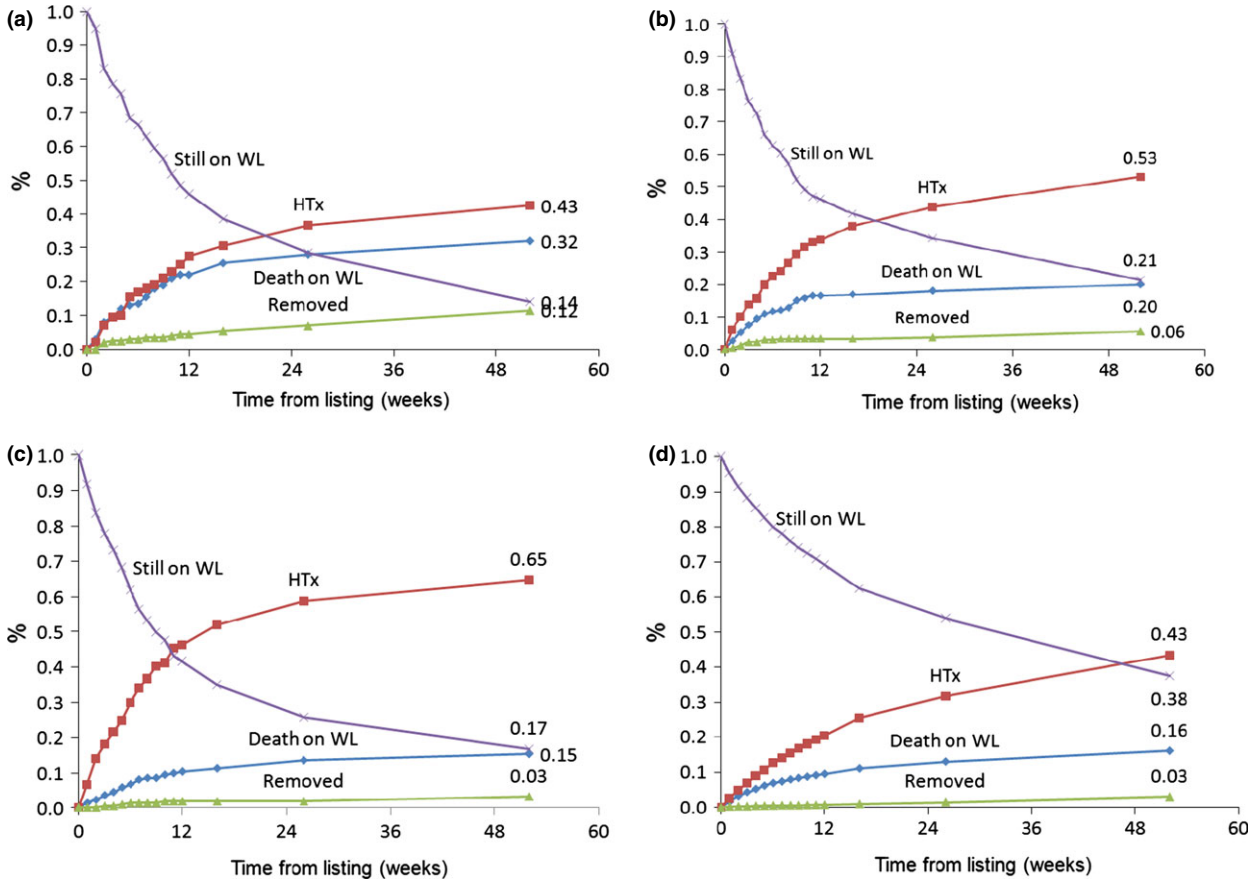

Figure 4 Waitlist outflow events for pediatric heart transplants (HT) candidates listed in Eurotransplant in period August 23, 2000—December 31, 2010. (a) Patients aged <1 year $n = 200$, (b) patients aged 1–10 years $n = 266$. (c) Patients aged 11–15 years $n = 221$. (d) Patients aged >16 years $n = 9932$.

types, no effect on waitlist mortality was observed. In addition, it is shown that the first 3 months after listing are crucial, as the pretransplant deaths mostly occur in this period.

Survival after transplantation increased over the years, and in almost a decade, the 1-year survival rates went up from 83% to 89%, and the 3-year rates increased from 81% to 85%. The primary disease of the patient was found to be the only risk factor for post-transplant mortality, where the HCM patients had the worst outcome.

An important limitation of this study is that our results are based on data which are derived from the ET registry.

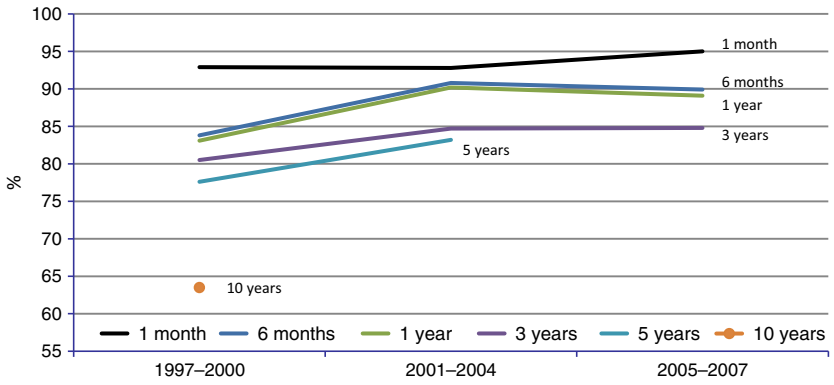

Figure 5 Post-transplant patient survival among pediatric heart transplant recipients 1997–2007.

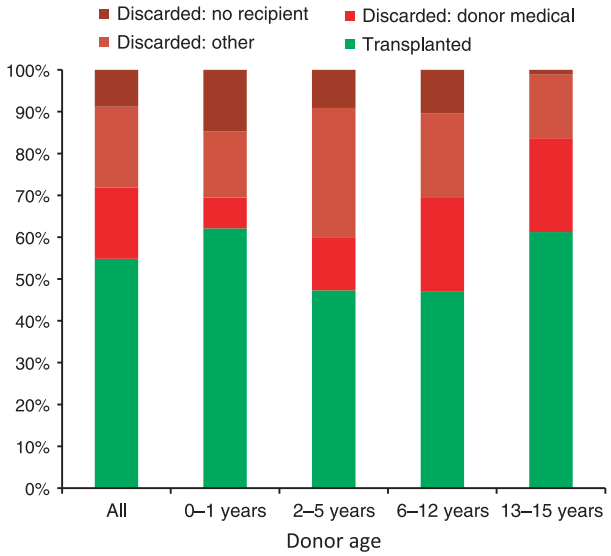

Figure 6 All offered pediatric heart donors reported to Eurotransplant (ET) in 2005–2009 [n = 363].

All eight countries collaborating in ET deliver data to this registry, where information necessary for allocation purposes—for example, severity of the heart disease and secondary organ dysfunction—are mandatory and complete, but detailed information on the patients' status post-transplant—for example, primary graft dysfunction—is not available. A further drawback of our study is the limited number of patients, which precludes any subanalysis. In addition to sharing pediatric donors even beyond the geographical area of ET, we think that knowledge on pediatric heart transplantation could be improved by joining all European registries into one pan-European organ transplant registry [14].

Similar to the results from Pediatric Heart Transplant Study (PHTS) [11], children with congenital heart diseases have the highest waitlist mortality in ET, with 31.6% of the listed patients dying within the first year after listing. In contrast to the PHTS data, pretransplant prognosis was different among the cardiomyopathy patients, where HCM patients were almost five times more likely to die prior to transplantation compared with DCM patients. As the number of patient series was very small, no further subanalysis was performed in children with varied DCM etiology [10]. Mortality in infants (<12 months old) awaiting heart transplantation is high throughout the world: In the USA, 23% died within 6 months after listing [12], this 6-month death rate was 28% in the ET cohort, while within 1 year after listing, 31% in the UK [15], 36% in Sweden [16] and 32% in the ET cohort died without a transplant.

In contrast to Canada, where ABO-incompatible (ABOi) transplants make up 40% of transplants in children under the age of 6 months [17], ABOi are less often (in one out of nine infants) used in ET as a potential measure to decrease waitlist mortality.

The proportion of patients transplanted from VAD increased in our ET cohort from 7.5% in the period 2002–2005 to 12.5% in the period 2006–2010. Although VADs are well-established treatment for end-stage heart failure in children that can increase the survival on the heart transplant waiting list [18], a close monitoring of severe adverse reactions remains warranted [19–22].

Ten-year pediatric post-transplant survival rates in our cohort and in the US are around 65% [11]. Post-transplant survival for infants was 88% at 1 year in our cohort and 81% in the Toronto cohort [20], 100% in the Newcastle series [14], and 85% in the US [23], while the collective data from the International Society for Heart and Lung transplantation (ISHLT) show a 1-year rate of 76% and a half-life of 19.2 years [24].

Our data show that discard rates for pediatric donor hearts are higher compared with the adult donors (45% vs. 38%). Regrettable, 9% of the <16 years donors and 17% of the <2 years donors are not used for transplantation due to the fact that there was no suitable candidate on the list. We

expect that by expanding the ABOi program and by creating one common ET waiting list for pediatric transplant candidates, the loss of these good quality donors and hence the waiting list mortality can be further reduced.

Conclusion

The ensuing increased routine to use assist devices for keeping patients alive until transplantation, and the improved medical care for heart failure patients has led to a reduction in death rates on the pediatric heart transplant waiting list 25% in 1997 to 18% in 2011. These death rates could further be reduced by expanding the ABOi program and by the installment of a ET waiting list.

Survival after HT has improved over the years and is now 88% at 1 year for children under 10 years and 85% for 11- to 16-year-old patients. Mechanical circulatory support is an optimal adjunct to pediatric patients on the ET waiting list to further increase these post-transplant survival rates. This should prompt the development of implantable devices with a spectrum of sizes suitable for the pediatric population.

Authorship

JMS: designed the study. JMS, AS, DG and EDV: analyzed the data. JMS, JT, MDP, EDW, AR, JB, GL, RH, HR and BM: contributed to the discussion.

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