

Heart Transplantation in the United States, 1999–2008

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Note on sources: The articles in this report are based on the reference tables in the 2009 OPTN/SRTR Annual Report. Table numbers are noted in brackets and may be found online at <http://www.ustransplant.org>.

This article features 1999–2008 trends in heart transplantation, as seen in data from the Organ Procurement and Transplantation Network (OPTN) and the Scientific Registry of Transplant Recipients (SRTR). Despite a 32% decline in actively listed candidates over the decade, there was a 20% increase from 2007 to 2008. There continues to be an increase in listed candidates diagnosed with congenital heart disease or retransplantation. The proportion of patients listed as Status 1A and 1B continues to increase, with a decrease in Status 2 listings. Waiting list mortality decreased from 2000 through 2007, but increased 18% from 2007 to 2008; despite the increase in waiting list death rates in 2008, waiting list mortality for Status 1A and Status 1B continues to decrease. Recipient numbers have varied by 10% over the past decade, with an increased proportion of transplants performed in infants and patients above 65 years of age. Despite the increase in Status 1A and Status 1B recipients at transplant, posttransplant survival has continued to improve. With the rise in infant candidates for transplantation and their high waiting list mortality, better means of supporting infants in need of transplant and allocation of organs to infant candidates is clearly needed.

Key words: Heart transplantation, OPTN, SRTR, survival

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Introduction

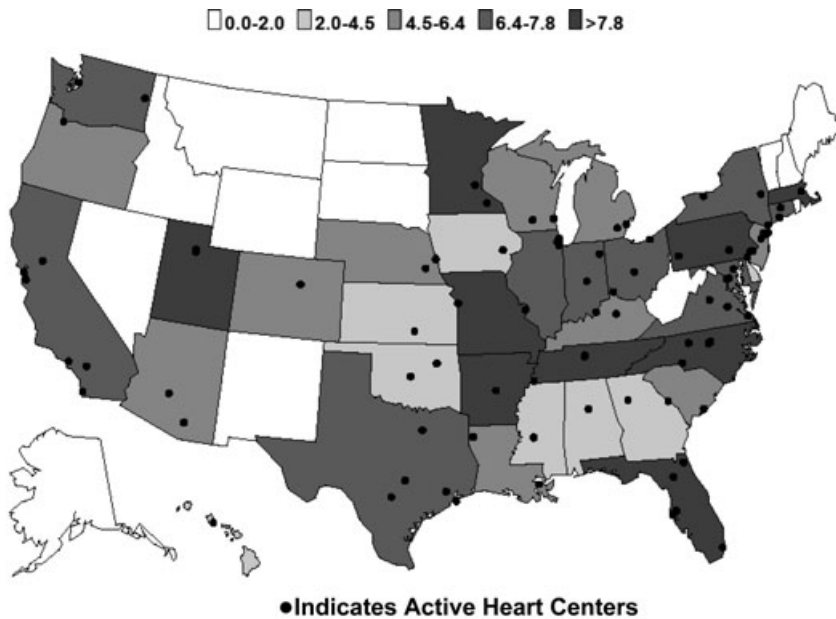
Despite improvements in medical and device therapy for heart failure, heart transplantation remains the best option for patients with end-stage heart failure who are deemed appropriate candidates. Although the incidence and prevalence of heart failure are increasing, the number of heart transplants performed has plateaued [Table 11.4]. In addition, the number of heart transplants performed per million population varied widely from state to state in 2008, from 0 in several states to >7.8 in nine states (Figure 1) [Table 11.5]. There are likely many reasons for this variability (including variable state demographics), but reasons which must be carefully considered include access to the waiting list, donor availability, utilization of available donor hearts, and deaths on the waiting list. Indeed, one of the program goals for organ allocation by the Organ Procurement and Transplantation Network (OPTN) is to reduce geographic variations in access to transplantation. Thus, in this year's report, where possible, information concerning geographic variability will be provided. Particular attention will also be paid to the increasing use of ventricular assist devices (VADs) in heart transplant candidates. Finally, an update will be provided concerning the effect of broader allocation of hearts for Status 1A and 1B candidates (which went into effect in July 2006) on waiting list mortality and transplant outcomes.

Heart Waiting List and Recipient Characteristics

Candidate characteristics

The characteristics of heart transplant candidates are reported for patients actively listed at the end of each calendar year from 1999 to 2008. The number of active candidates declined 32% over the decade, from 2477 to 1684 [Table 11.1a]. Of note, a 20% increase in active candidates was seen from 2007 to 2008 (1406 and 1684, respectively).

When examined by age, there was a modest increase in the proportion of pediatric patients on the waiting list (see 'Pediatric Transplantation' section for details), as well as those over 65 years (from 9% to 14%) [Table 11.1a]. The demographics of the waiting list have changed slightly, with a decrease in the proportion of white candidates (from 79% to 73%) and an increase in the proportion of both African American (from 13% to 18%) and Hispanic/Latino candidates (from 6% to 7%). Candidate gender has shifted from 21% to 24% female. A small increase in candidates



●Indicates Active Heart Centers

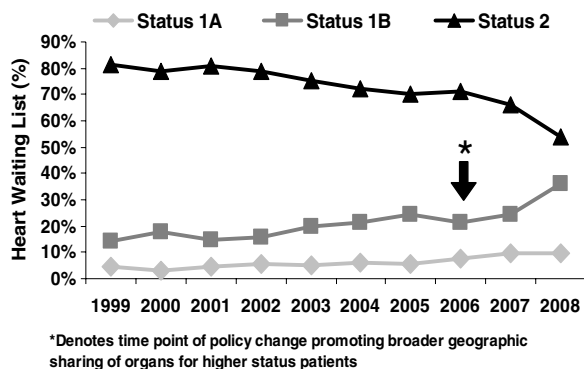
Figure 1: 2008 incidence of heart transplants per 1 million population.

Source: 2009 OPTN/SRTR Annual Report, Table 11.5.

who are recipients of prior solid organ transplants was seen (from 3% to 7%), mostly in candidates waiting for heart retransplant (from 3% to 6%). The proportion of candidates with congenital heart disease has increased (4% to 9%), and the proportion of candidates with coronary artery disease has decreased (48% to 40%), with the proportion of other diagnosis groups remaining similar (currently, primary cardiomyopathy in 42% and valvular disease in 2%) [Table 11.1a].

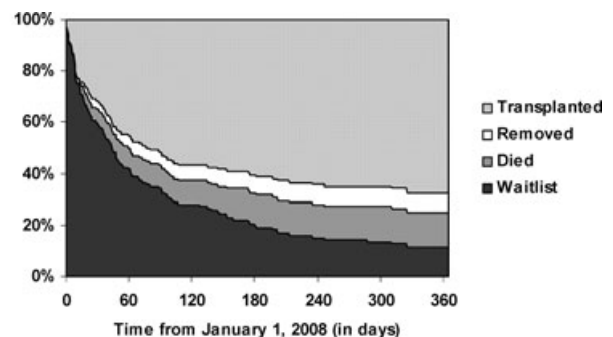
The criteria by which patients are assigned a waiting list status (1A, 1B and 2) have not changed substantially since 1999. (See OPTN policies 3.7.3 and 3.7.4 at <http://optn.transplant.hrsa.gov/PoliciesandBylaws2/policies/pdfs>

/policy_9.pdf). There has been a slow but persistent increase in the proportion of Status 1A and 1B patients and a decline in Status 2 patients over the last several years (Figure 2) [Table 11.1a]. Of patients on the waiting list on January 1, 2008 (regardless of waiting time accrued), the following observations can be made: (1) among Status 1A patients, 16% were 'downgraded' to Status 1B and 46% were transplanted by 60 days. Mortality for those patients who did not undergo transplantation by 30 and 60 days was 5% and 7%, respectively. At 365 days, 15 patients (11%) remained on the waiting list; 4 remained Status 1A, 7 Status 1B and 4 inactive; 18 patients (14%) had died (6 Status 1A, 2 Status 1B and 10 inactive) (Figure 3). (2) Among 1B patients, 11% were 'upgraded' to 1A, and 25% were transplanted by 60 days. Mortality for Status



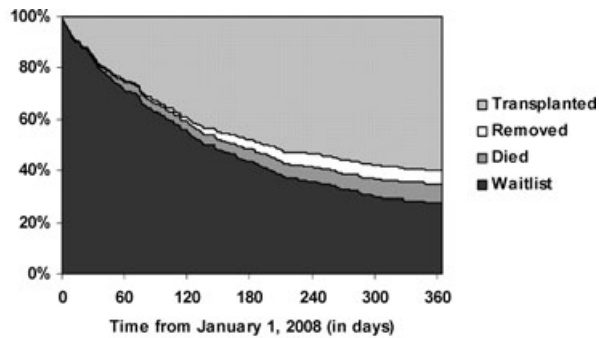
Source: 2009 OPTN/SRTR Annual Report, Table 11.1a.

Figure 2: Status of heart transplant waiting list candidates, 1999-2008.



Source: SRTR analyses, data as of May 1, 2009

Figure 3: Condition of status 1A patients on heart waiting list as of January 1, 2008, by day.



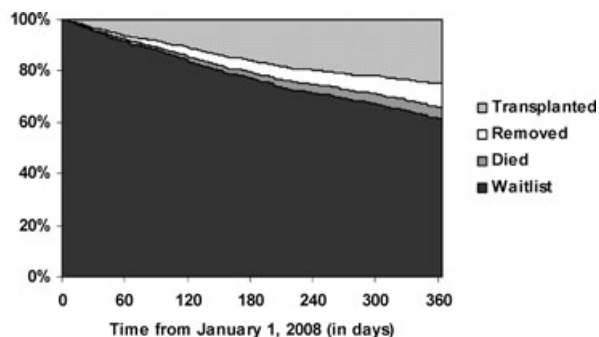
Source: SRTR analyses, data as of May 1, 2009

Figure 4: Condition of status 1B patients on heart waiting list as of January 1, 2008, by day.

1B patients who did not undergo transplantation by 30 and 60 days was 1% and 3%, respectively. At 365 days, 94 patients (27%) remained on the waiting list (8 Status 1A, 59 Status 1B, 1 Status 2 and 26 inactive); 24 patients (7%) had died (5 Status 1A, 7 Status 1B, 1 Status 2 and 11 inactive) (Figure 4). (3) Only 6% of Status 2 patients were transplanted within 60 days, with a waiting list mortality of only 1%, although 4% had been upgraded to Status 1A or 1B [Table 11.2b]. At 365 days, 549 patients (59%) remained on the waiting list (9 Status 1A, 61 Status 1B, 364 Status 2 and 115 inactive); 42 patients (5%) had died (1 Status 1A, 2 Status 1B, 21 Status 2 and 18 inactive) (Figure 5). During the last decade, there has been a slight decrease in the percentage of active patients waiting for 1 year or greater, from 40% in 1999 to 33% in 2008 [Table 11.1a]. The number of inactive patients has remained relatively high (38% in 2008 vs. 37% in 1999) [Table 11.1b].

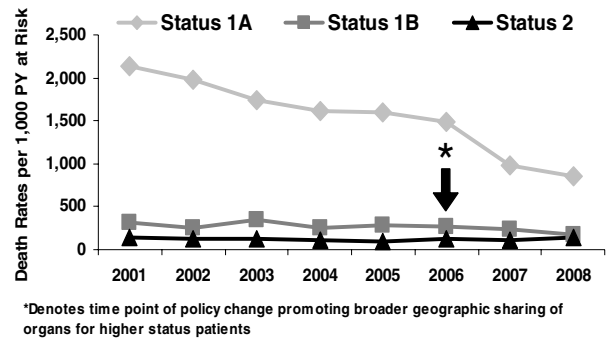
Discussion

The increase in Status 1A and 1B and decline in Status 2 patients over the past decade is likely due to increased utilization of ventricular assist devices (VADs) as a bridge



Source: SRTR analyses, data as of May 1, 2009

Figure 5: Condition of status 2 patients on heart waiting list as of January 1, 2008, by day.



Source: 2009 OPTN/SRTR Annual Report, Table 11.3.

Figure 6: Annual death rates per 1000 patient-years on the heart waiting list by status, 2001–2008.

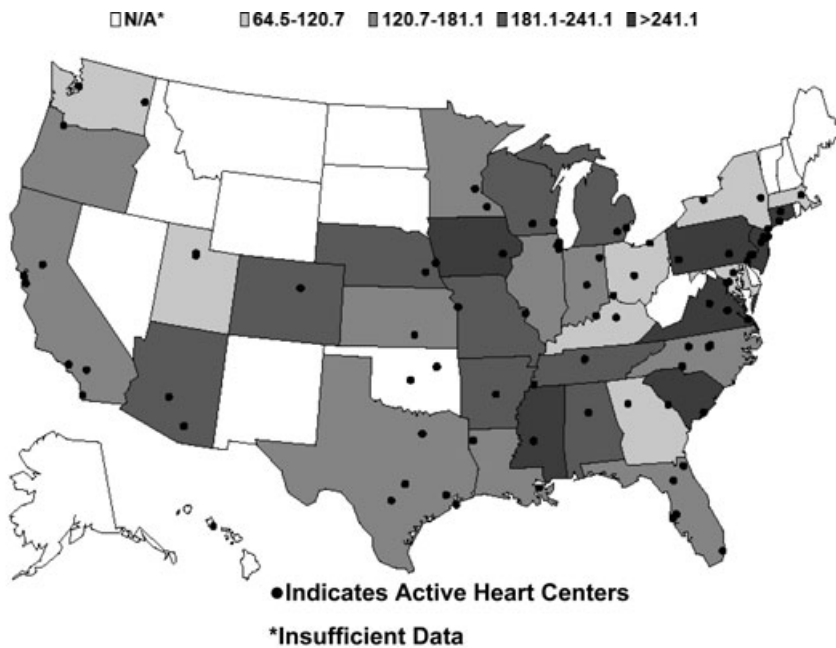
to transplant (as detailed in the ‘Patient Care Issues’ section of this report). Also, many centers do not actively list patients who are unlikely to receive an organ offer unless their clinical status deteriorates to Status 1A or 1B, particularly since the 2006 implementation of policy promoting broader sharing. In addition, there is doubt that all patients who are classified as ‘stable’ Status 2 receive survival benefit from transplantation.

Deaths on the waiting list

The death rate increased from 144 per 1000 patient-years at risk in 2007 to 170 per 1000 patient-years at risk in 2008 [Table 11.3]. However, the overall death rate of patients awaiting heart transplantation has decreased over the past decade, from 199 per 1000 patient-years at risk in 1999 to 170 per 1000 patient-years at risk in 2008. Reduced death rates over the decade were seen across all adult age groups and major categories of gender, blood type (with too few in blood type AB for meaningful analysis) and race/ethnicity, with the exception of African American candidates. Death rates also decreased by primary diagnosis categories except for congenital heart disease [Table 11.3]. When examined by urgency status, the decline in waiting list mortality was evident across Status 1A, 1B and 2 patients, although it was most pronounced for patients listed as Status 1A (Figure 6). Despite this encouraging decline in waiting list mortality overall, the waiting list death rate varied widely by state in 2008, from 65 in Oklahoma to 652 in the District of Columbia (among states with adequate cohorts for analysis) (Figure 7) [Table 11.3].

Discussion

The more marked decline in waiting list mortality for Status 1A and 1B patients likely reflects the impact of the increased use of left ventricular assist devices (LVADs), and perhaps, for 2007 and 2008 data, the regional allocation policy for Status 1A and 1B recipients that began in July 2006. However, the marked variability in waiting list deaths among states suggests that organs are still not getting to those who need them most.

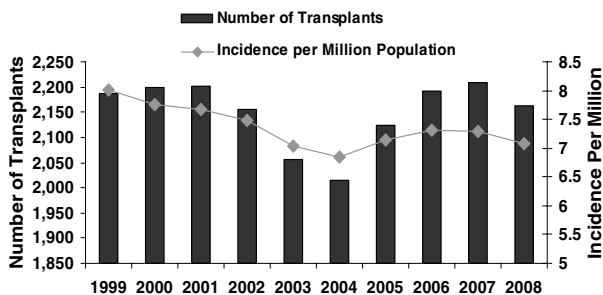


Source: 2009 OPTN/SRTR Annual Report, Table 11.3.

Figure 7: 2008 annual death rates on heart waiting list.

Recipient characteristics

The number of heart transplants performed in the United States has varied by 10% over the past decade, from a low of 2015 in 2004 to a high of 2209 in 2007. While the number of heart transplants had increased from 2004 to 2007, there was a 2% decrease in 2008 (Figure 8) [Table 11.4]. Over the last 10 years, there was a 12% decrease in the rate of heart transplants per million U.S. residents, although this trend appears to have leveled off recently (Figure 8) [Table 11.5]. Among patients transplanted, there has been a decrease in transplants in the 50–64 year age group, with a concomitant rise in transplants performed in the very young and older patients. The distribution of organs between genders had been quite stable, with a slight increase in the number of grafts going to women (28%) in

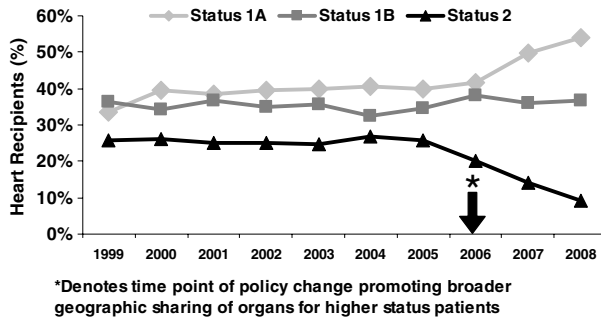


Source: 2009 OPTN/SRTR Annual Report, Tables 11.4 and 11.5.

Figure 8: Number of heart transplants and incidence of transplant per million population, 1999–2008.

2008. There has been a 17% reduction in the number of white recipients, with a concomitant rise in transplants performed in the other ethnicity/racial groups. A drop of 26% was seen in the number of patients transplanted with a diagnosis of coronary artery disease, while there has been an increase in the proportion of patients transplanted for primary cardiomyopathy and congenital heart disease during the same period [Table 11.4]. Retransplantation was the indication for transplantation in 4% of the 2008 cohort (see further details in the ‘Retransplantation’ section of this report). The overall prevalence of heart transplant recipients has risen 24% from 15 593 in 1999 to 19 308 in 2007 [Table 11.16].

The new status classification system was established between 1999 and 2008. Within this period, the distribution of patients among the different status groups at the time of heart transplantation has shifted toward the more urgent status levels. In 1999, patients transplanted as Status 1, 1A, 1B and 2 accounted for 4%, 34%, 36% and 26% of transplants respectively. In 2008—indicative of the new system and the shift in levels—the proportions for Status 1A, 1B and 2 were 54%, 37% and 9% respectively. There was a marked increase in Status 1A transplants and a decrease in Status 2 transplants since broader allocation for Status 1A and 1B candidates began in July 2006 (Figure 9) [Table 11.4]. In the years before and after this policy change, the percentage of transplant recipients with organs having a cold ischemia time less than 180 min decreased by only 3% (39% in 2005 vs. 36% in 2008). From 2005 to 2008, the proportion of donor organs with cold ischemia times over 270 min did not change, and the



Source: 2009 OPTN/SRTR Annual Report, Table 11.4.

Figure 9: Waiting list status of heart transplant recipients at transplant, 1999–2008.

increase in the proportion over 180 min was 5% [Table 11.4].

Heart Utilization

At year end 2008, 1684 patients were on the active heart waiting list, representing a 20% increase in list size from 2007 [Table 11.1a]. While list size increased, the number of transplants actually decreased by 3% during this same time period [Table 1.7]. The reported annual death rate for patients on the heart waiting list in 2008 was 170 per 1000 patient-years at risk, the highest for all organ-specific categories [Table 1.6].

There were 16 070 deceased organ donors in the United States during 2007 and 2008 [Table 1.1], and 28% of the time, a heart was recovered and transplanted. Since so much variability exists in donor type (standard, extended criteria and donation after cardiac death), it is imperative to look at the standard criteria donor (SCD) category when evaluating heart utilization, as most hearts are recovered and transplanted from this group. For this analysis, OPO donor heart utilization was defined as the percent of donor hearts recovered and eventually transplanted (within or outside of the OPO) from SCD donors where at least one organ (kidney, pancreas, liver, intestine, heart or lung) was recovered for transplantation. During 2007 and 2008, there were 10 414 standard criteria organ donors where at least one organ was recovered for transplant. From this cohort, a heart was utilized 42% of the time (SRTR analyses, data as of May 1, 2009).

A review of heart utilization by Organ Procurement Organization (OPO) donor service area (DSA) during 2007 and 2008 reveals substantial variability. SCD donor heart utilization varied from 11% to 55%. Spearman's Correlation Coefficient was used to assess whether there were OPO donor or other characteristics that correlate with the percent of hearts transplanted. Variables considered included: race, gender, donor age, cause of death, number of heart

transplant programs in the DSA and number of patients on the waiting list in the DSA at year end. An increased number of heart transplant programs and patients on the waiting list correlated with a trend for increased heart utilization ($p = 0.04$, $p = 0.004$ respectively). None of the other donor characteristics listed above as included in the analysis were significantly associated with heart utilization.

While a positive correlation exists between percent heart utilization from SCD donors and the number of transplant centers in the DSA, the top three OPOs in percent heart utilization had two or fewer heart centers in their DSA and still averaged greater than 50% utilization. DSAs with only two heart centers varied from 24% to 55% utilization, and those with one center varied from 11% to 53%. Of the programs with three transplant centers in their DSA, the range of heart utilization was 33% to 53%. Similar variability exists between OPTN regions. With the 2006 allocation change increasing regional sharing for Status 1A and 1B candidates, one would expect utilization within regions to be somewhat similar, yet surprisingly, marked variability still exists (Figure 10).

Discussion

Based on the analysis outlined above, it appears highly unlikely that donor quality or the number of transplant centers or heart transplant candidates in a DSA can entirely explain the wide variability in heart utilization. Best practices within the DSA community need to be identified and disseminated in order to optimize heart utilization in all DSAs to achieve a further decrease in deaths on the heart waiting list.

Heart Transplant Outcomes

Patient survival, adjusted for age, gender, ethnicity/race and diagnosis across the entire cohort of patients is 93%, 89%, 75% and 56% at 3 months, 1, 5 and 10 years, respectively [Table 11.12]. Recent-era adjusted patient survival after heart transplantation at 3 months, 1 year and 5 years posttransplant is similar across the adult range of patient ages, but there is a marked decrease in survival at 10 years for patients 65 years and older (55%, 59%, 55% and 46%, for age groups 18–34 years, 35–49 years, 50–64 years and 65 years and older, respectively) (Figure 11) [Table 11.12].

At all time points, survival is lower for women than for men by approximately 2–3% (i.e. 5-year survival for men transplanted in 2002 or after is 76%, whereas survival for women in the same era is 73%). In addition, despite similar 3-month survival, medium to long-term survival for African Americans is lower than in other ethnic/racial groups (10-year survival is 59% and 43%, respectively, for whites and African Americans) [Table 11.12]. There is also some divergence in survival based on primary diagnosis. Whereas 1-, 5- and 10-year survival for patients with cardiomyopathy

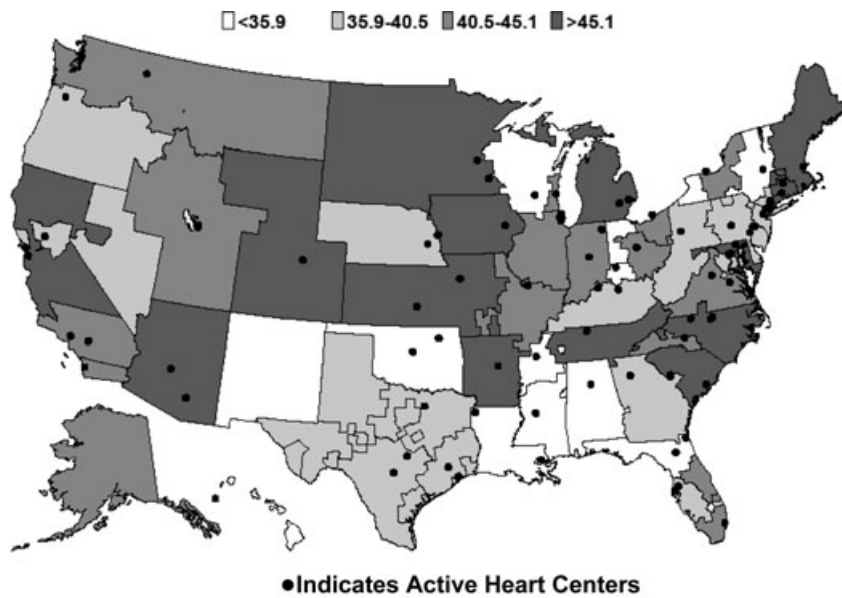


Figure 10: Donor utilization—number of hearts recovered and transplanted per 100 standard-criteria donors by donor service area in 2007–2008.

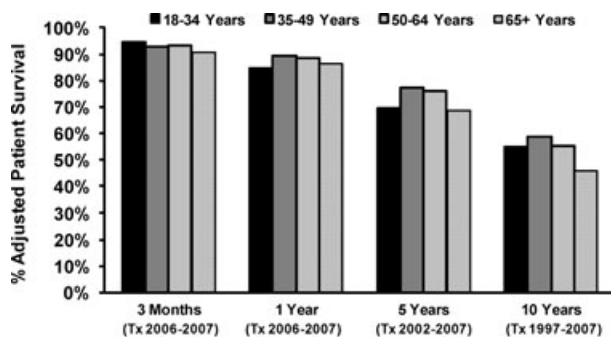
Source: SRTR analyses, data as of May 1, 2009

is 91%, 77% and 59%, the survival for patients with congenital disease is 74%, 64% and 53% respectively.

With the exception of donors in the <1 and 1–5 age groups, recipient survival decreases with each progressively older donor group. One-year survival among heart recipients transplanted within 2006–2007 was 96%, 92%, 90%, 86% and 83% among donor age groups 6–11, 12–17, 18–34, 35–49 and 50–64, respectively. There were not enough transplants from donors over the age of 65 for a meaningful analysis. Ischemia time also appears to affect patient survival. Three-month, 1-year and 5-year survival decrease with increasing cold ischemic time with more pronounced drops after 270 min; however, 10-year patient survival does not appear to differ by cold ischemic time. One-year survival by cold ischemic time among heart recipients transplanted in 2006 and 2007 was 92%, 90%, 89%, 84%, 84%

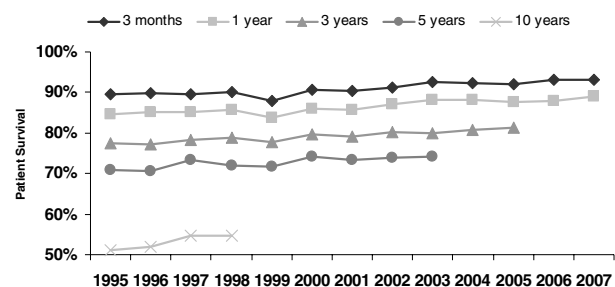
and 79% for 0–90, 91–180, 181–270, 271–360, 361–480 and 481+ min, respectively [Table 11.14].

There have been substantial improvements in survival over time as experience has accrued (i.e. 3-month survival has improved from 86% to 93% in patients transplanted in 1987 and 2007, respectively, and 10-year survival has improved from 46% to 55% for patients transplanted in 1987 and 1998, respectively) (Figure 12) [Table 11.13]. More recent patients have not yet accrued enough time following transplantation to determine 10-year survival. In the first year after heart transplantation, death rates have steadily decreased, from 191 deaths per 1000 patient-years at risk in 1999 to 123 deaths per 1000 patient-years at risk in 2007 (Figure 13) [Table 11.7]. For all status groups since 1999 (the year the current status system for allocation was implemented), there has been a decrease in death rates in



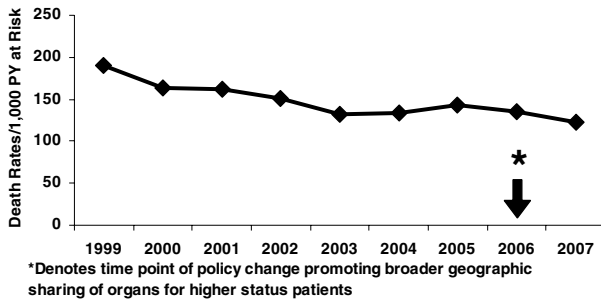
Source: 2009 OPTN/SRTR Annual Report, Table 11.12.

Figure 11: Posttransplant patient survival by age.



Source: 2009 OPTN/SRTR Annual Report, Table 11.13.

Figure 12: Adjusted short- and long-term survival of heart recipients, by year of transplant, 1995–2007.



Source: 2009 OPTN/SRTR Annual Report, Table 11.7.

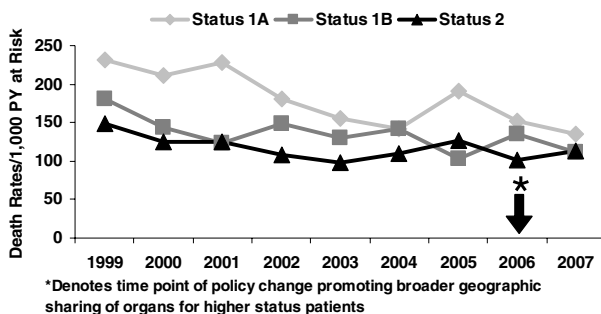
Figure 13: Annual death rate per 1000 patient-years at risk for recipients during first year after heart transplantation, 1999–2007.

the first year after heart transplantation (Figure 14). Importantly, a trend to a decrease in early posttransplant deaths for Status 1A recipients was seen between 2005 and 2007, when broader allocation of organs began (although longer-term follow-up and data from additional recipients is necessary to confirm this trend) [Table 11.7]. The decrease in posttransplant death rates occurred in both sexes, although females consistently have a modestly higher death rate. Death rates for whites continue to improve, however this trend is not as apparent in more recent years among other ethnicity/race groups, including African Americans, Asians, or Hispanic/Latinos (Figure 15) [Table 11.7].

Patient Care Issues

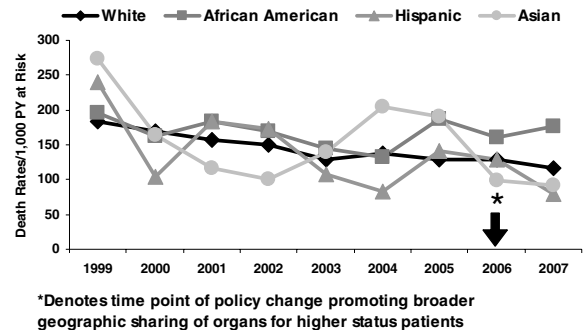
Ventricular assist devices as a bridge to transplant

Only a tiny fraction of patients with end-stage heart failure are treated by heart transplantation, despite aggressive organ donor initiatives. In addition, for every five patients who receive a heart transplant, about one patient dies on the waiting list (441 deaths on the waiting list vs.



Source: 2009 OPTN/SRTR Annual Report, Table 11.7.

Figure 14: Annual death rate per 1000 patient-years at risk during first year after heart transplantation by status, 1999–2007.



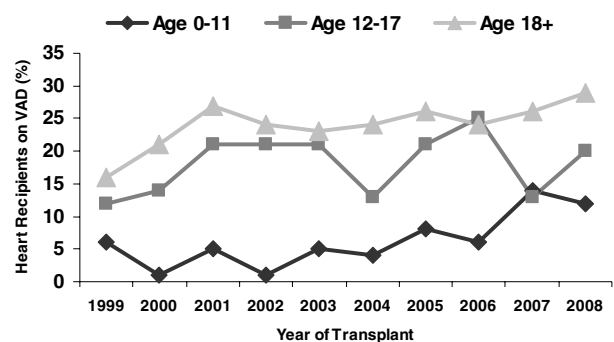
Source: 2009 OPTN/SRTR Annual Report, Table 11.7.

Figure 15: Annual death rates per 1000 patient-years during first year following heart transplantation by race/ethnicity, 1999–2007.

2163 patients transplanted in 2008) [Tables 1.6 and 11.4]. Currently, 68% of heart transplant recipients require life support (including intravenous medications, mechanical ventilation, intra-aortic balloon pumps, extracorporeal life support, total artificial hearts, or VADs) as a bridge to transplant [Table 11.4]. VADs are now routinely used as bridges to transplant, and increasingly as ‘bridges to decision’ for patients who may need time and circulatory support while determination of transplant suitability is established.

The proportion of adult patients undergoing heart transplantation off of a ventricular assist device has risen dramatically over the past decade, from 16% in 1999 to 29% in 2008. The trend has been similar in younger patients, with 12% of recipients younger than 11 years of age and 20% of adolescents aged 12–17 supported with a VAD in 2008 (Figure 16) (SRTR analyses, data as of May 1, 2009).

The increase in utilization of VADs has led to a few notable trends in heart recipient characteristics. Although the proportion of patients transplanted off some form of life



Source: SRTR analyses, data as of May 1, 2009

Figure 16: Heart recipients on a VAD at time of transplantation by age and year, 1999–2008.

support has remained relatively stable, the proportion transplanted from a nonhospital setting has increased from 39% to 48%, representing primarily ambulatory, out-of-hospital VAD-supported patients [Table 11.4]. To place this in perspective, between July 2006 and July 2008, the proportion of patients with a VAD at the time of listing was 13%, while the proportion of patients with a VAD ever while listed was 20% (1).

Discussion

Evidence in support of VAD use in heart transplant candidates is largely observational, demonstrating reduced mortality with VAD use in inotrope-dependent heart transplant candidates and derived from a study of VAD use as destination therapy (2). However, as VAD utilization has increased, concerns have been raised about the effect on posttransplant outcomes. An OPTN report found a higher mortality in VAD-supported patients when compared to non-VAD Status 1 patients (3) at 6 months and 5 years after transplant. Although these findings were adjusted for risk factors at the time of transplant, important differences at the time of VAD insertion were not addressed. In particular, many patients receive VADs as a 'bridge to candidacy' in the hopes of improving end organ function, pulmonary vascular resistance, or medical compliance. In addition, this report is now largely historical, since it included early, first-generation devices less frequently used today. A more recent report from a single center (4), and an abstract presented at the American Transplant Congress in 2009 using the OPTN database (5), have shown equivalent early posttransplant outcomes whether or not patients received a VAD as a bridge to transplant.

Shortcomings in first-generation VADs (volume displacement, pulsatile pumps) have led to development of enhanced designs, with the goal of improved durability (longer possible support times) and fewer complications. A clinical trial of the HeartMate II LVAD demonstrated improved quality of life and functional status in a group of patients supported using the device as a bridge to transplant (6). This technology has recently gained U.S. Food and Drug Administration (FDA) approval for bridge to transplantation.

Ventricular assist technology is in rapid evolution and may provide a realistic alternative to transplantation in the future. However, it has been difficult to integrate VAD use as a bridge to transplant in heart transplant allocation policy because of the paucity of information prospectively collected for the OPTN database; rapidly changing technology and outcomes compound this difficulty. Additional data from other sources, such as the Interagency Registry for Mechanical Assisted Circulatory Support (INTERMACS), will add to our future knowledge base, and may take us closer to an allocation method similar to the Lung Allocation Score, which defines organ allocation based on risk of death without transplant and expected survival if

transplanted. In the not-too-distant future, improved VAD outcomes may lead to a lower priority for VAD-supported patients and a higher priority for patients with other diseases, such as restrictive, congenital, or hypertrophic cardiomyopathy, or patients with electrical or coronary instability.

Immunosuppression for heart transplant recipients

Immunosuppression for heart transplant recipients has continued to evolve over the past decade. Induction therapy, primarily in the form of equine antithymocyte globulin (Atgam[®]) or muromonab-CD3 (OKT3[®]), was used for 34% of patients in 1999, increasing to 52% in 2008, although the drugs used have shifted toward rabbit anti-lymphocyte globulin (Thymoglobulin[®]) in 18%, or monoclonal antibody therapy directed against the IL-2 receptor [daclizumab (Zenapax[®]) or basiliximab (Simulect[®])] in 25% of heart recipients [Table 11.6a].

The overwhelming majority of transplant recipients continue to be discharged on triple drug therapy consisting of a calcineurin antagonist, mycophenolate mofetil/mycophenolic acid or other antimetabolite, and steroids. In 2008, the most common discharge regimen, by far, was tacrolimus, mycophenolate mofetil/mycophenolic acid and steroids (58% of transplant recipients) [Table 11.6d]. The use of the mammalian target of rapamycin (mTOR) inhibitors sirolimus (Rapamune[®]) or everolimus (Certican[®]) at discharge, in various combinations with other agents, is only 3%, likely out of concern for impaired wound healing in the immediate postoperative period [Table 11.6e].

At 1 year following transplantation, triple drug therapy with tacrolimus, mycophenolate mofetil/mycophenolic acid and steroids remains the predominant treatment regimen (approximately 37% of heart recipients) [Table 11.6f]. Tacrolimus use in any combination is now 68%, while cyclosporine use is only 27%. Mycophenolate mofetil/mycophenolic acid is the most common antimetabolite, utilized in 80% of patients. Since 1998, there has been a small but important trend toward steroid-free drug regimens by 1 year following transplantation (38% of 2007 recipients). The use of either sirolimus or everolimus between discharge and 1-year posttransplant is approximately 10%, reflecting the fact that mTOR inhibitors may have utility in preventing and/or retarding transplant coronary artery disease [Table 11.6g].

A declining number of recipients have received treatment for rejection during the first year following transplantation (19% in 2007 compared with 42% in 1998). The overwhelming majority of rejection episodes are treated with steroids (90%), while approximately 17% are treated with antibody therapy, most frequently with rabbit anti-lymphocyte globulin [Table 11.6i].

Pediatric Transplantation

Pediatric heart transplant candidates and recipients (<18 years of age) represent a distinct population in comparison with adults. Important differences exist in etiologies of organ failure, the need for more complex and technically challenging surgical procedures, developmental effects on pharmacokinetic properties of immunosuppressive agents, immunological aspects of transplantation in the developing immune system and susceptibility to certain posttransplant complications, most notably infectious diseases and lymphoproliferative disorders. This section focuses on pediatric heart transplantation, drawing attention to differences from adult candidates and recipients.

Candidate characteristics

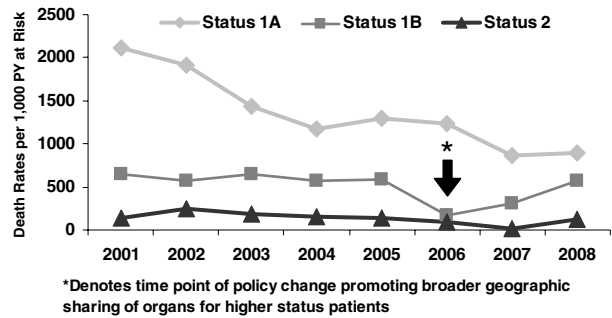
The number of pediatric patients awaiting heart transplantation has been relatively steady over the past 10 years, with 122 actively awaiting transplantation at the end of 2008 [Table 11.1a]. Although the absolute number of pediatric candidates on the active waiting list did not change over the last decade, there has been a modest rise in the total proportion of active candidates that are less than 18 years of age, rising from 5% at the end of 1999 to 7% at the end of 2008. The number waiting was similar for age groups < 1 year (n = 30), 1–5 years (n = 27), 6–11 years (n = 27) and 12–17 years (n = 38). However, for any single 12-month age group, infants (0–1 year of age) make up, by far, the largest group of candidates. Infants (<1 year) represented 40% (223 of 558) of all new pediatric registrations in 2008 (SRTR analyses, data as of May 1, 2009) [Table 15.3].

The diagnoses leading to listing for transplantation vary by age. For infant candidates, the indication for placement on the waiting list is a congenital heart anomaly in 65% of patients (SRTR analyses, data as of May 1, 2009). In older children and adolescents, cardiomyopathy is the leading indication for transplantation; however, congenital cardiac anomalies continue to account for a substantial minority of transplants (30% in the 12–17 year age group). These observations are important because complex cardiac anatomy and small size add to the risks and complexity of VAD support in very young children. Difficulty supporting young patients with complex congenital heart disease undoubtedly contributes to their high waiting list mortality (see below).

Analysis of waiting list status reveals a steady rise in the proportion of candidates who are listed as Status 1A at the time of listing. In 2008, 83% of infants, 65% of patients age 1–5, 62% of patients age 6–11 and 58% of adolescents were listed as Status 1A (SRTR analyses, data as of May 1, 2009). Thus, initial listing as Status 1A is more common in younger candidates, especially infants.

Deaths on the waiting list

Waiting list mortality for pediatric heart transplant candidates varies with age. Most deaths on the waiting list oc-



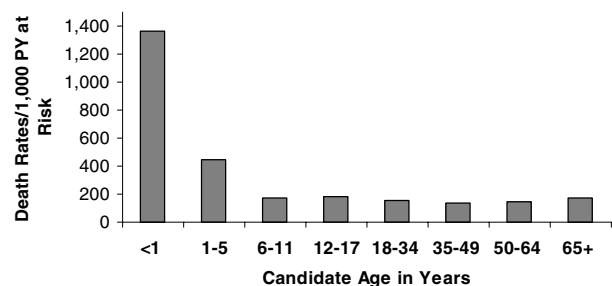
Source: SRTR analyses, data as of May 1, 2009

Figure 17: Annual death rate for pediatric candidates (<18 years) by status on the heart waiting list.

cur in Status 1A patients, with very low 1-year mortality for Status 2 patients (Figure 17) (SRTR analyses, data as of May 1, 2009). Infants have the highest waiting list mortality of any age group (adult or pediatric) (Figure 18) [Table 11.3]. The annual death rate was 1361 per 1000 patient-years at risk for infants in 2008, compared to 170 for all age groups combined (adult and pediatric). The second highest waiting list annual death rate (among all age groups, pediatric and adult) was for the 1- to 5-year age group at 442 per 1000 patient-years at risk. For children above 6 years of age, the waiting list death rates are broadly comparable to those for adults. In general, there has been no important change in annual death rates over the last decade among pediatric candidates, except for in the 12- to 17-year age group, which has seen a fall in annual death rate on the waiting list from 372 per 1000 patient-years at risk in 1999 to 180 in 2008. It seems likely that this reflects the increasingly successful use of VADs to support critically sick adolescents to transplantation over the last decade.

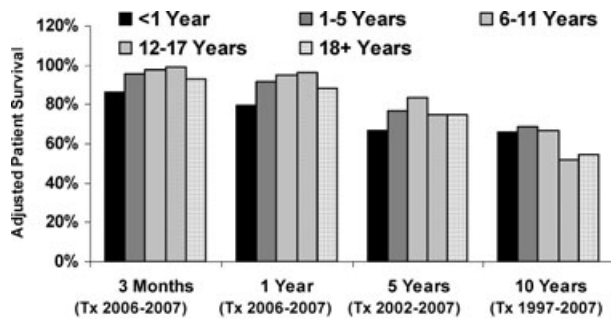
Recipient characteristics

Over the past 10 years, children have accounted for an increasing percentage of all heart transplants (12% in 1999, 17% in 2008) [Table 11.4]. There has been a steady increase in the number of pediatric transplants, from 252 in



Source: 2009 OPTN/SRTR Annual Report, Table 11.3.

Figure 18: 2008 wait list mortality by age.



Source: 2009 OPTN/SRTR Annual Report, Table 11.12.

Figure 19: Posttransplant patient survival by age.

1999 to 366 in 2008. The largest increase has occurred in children less than 6 years of age. The rate of transplantation per 1 million population remains higher for infants than for any other age group, at 23 [Table 11.5]. For all other pediatric age groups, the rates were generally less than for adults and ranged from 3 to 5 per million population. The high rate of transplantation in these very young children reflects the incidence of severe symptomatic congenital heart disease in the first year of life, as well as the relatively high incidence of cardiomyopathy in this age group. At the time of transplantation, 96% of infants, 76% of those age 1–5, 80% of those aged 6–11 and 78% of adolescents were Status 1A (SRTR analyses, data as of May 1, 2009). As with initial wait-listing status, infants were most likely to be Status 1A at the time of transplantation compared with the other pediatric age groups.

Heart transplant outcomes

Death rates per 1000 patient-years at risk during the first year after transplantation for 1999–2007 were generally highest for the infant age group compared with all other age groups (adult and pediatric), while rates were generally lower for most other pediatric age groups. The infant annual death rate for 2007 recipients was 230 deaths per 1000 patient-years at risk compared with 123 for all age groups combined [Table 11.7]. Rates for the pediatric age groups 1–5 years, 6–11 years and 12–17 years were 85, 35 and 60 deaths per 1000 patient-years at risk, respectively. Importantly, there is no evidence of a reduction of first-year annual death rates among infant heart recipients over time, but reductions have been observed for all other pediatric age groups.

Adjusted patient survival assessed through time-to-event analyses reveals trends different from adults. The lowest 3-month and 1-year survival rates among all groups (including adults) is for recipients less than 1 year of age (86% and 79% respectively) (Figure 19) [Table 11.12], likely related to the technical challenges posed in surgical procedures for these very young patients, many of whom have complex congenital heart disease. Interestingly, these same

recipients have among the highest 10-year survival (66%), likely related to the immaturity of the immune system in infancy and the reduced prevalence of posttransplant coronary artery disease (Figure 19). Beyond infancy, short-term survival is excellent in all other pediatric age groups, with 1-year survival exceeding that for all adult age groups (1-year survival of 92–96% among pediatric recipients from 1–17 years compared with 1-year survival of 85–89% among adult recipients of various age groups) [Table 11.12]. Of interest, the 1–11 year age groups maintain late graft survival rates distinctly superior to those of adults (about 10% higher), while recipients in the 12- to 17-year age group have late graft outcomes worse than all other age groups (10-year survival 46%), with the exception of the over 65 year-old population (10-year survival 45%) (Figure 19) [Table 11.8]. It is widely speculated that these poor outcomes in adolescent recipients reflect nonadherence to their medical regimens.

Ventricular assist device use in children

It has been possible to support most adolescent candidates with adult VADs, most commonly with pneumatic devices in a paracorporeal configuration, and the number of children receiving VADs in the 12- to 17-year age group has been relatively stable over the last 10 years. In 2008, 20% of 12–17 year-olds were supported with a VAD at the time of transplant (Figure 16) (SRTR analyses, data as of May 1, 2009). Results in this age group have been encouraging when the underlying diagnosis is cardiomyopathy rather than congenital heart disease (7). The age group with the fastest-growing use of VADs is the under 12-year-old population, where 1% to 5% of recipients were supported with a VAD in 1999 to 2004, compared with 12% of heart recipients in 2008. This trend is likely the direct effect of availability of devices designed for pediatric use and made available through ‘compassionate use’ protocols. Most programs have supported children under 25 kg with the Berlin Heart (EXCOR[®], Berlin Heart GmbH, Berlin, Germany), which has been developed in various sizes. Future reports will evaluate the efficacy of pediatric VADs as a bridge to transplantation in small children, including infants. Encouragingly, a number of new VADs designed specifically for pediatric use are under development, supported by a contract from the National Heart, Lung and Blood Institute of the National Institutes of Health (8).

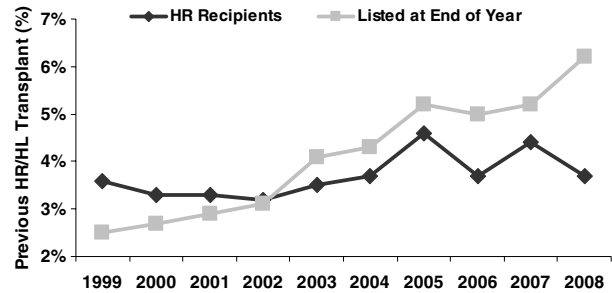
ABO-incompatible heart transplants in infants

A unique feature of pediatric transplantation is the growing use of ABO-incompatible heart transplantation (ABO-I) among infants. The percentage of eligible infants listed for an ABO-I heart increased from 0% before 2002 to over 50% in 2007. The strategy was developed by West and colleagues in Toronto, and relies on the observation that isoheamagglutinins (anti-A and anti-B antibodies) generally develop late in infancy (9). When transplantation is performed prior to the natural development of antibodies against blood groups antigens, B cell tolerance appears to

develop, and antibodies are usually not produced during long-term follow-up. International outcomes to date suggest no differences in adjusted posttransplant survival between infants receiving compatible versus incompatible blood group heart transplants (10). It was hoped that introduction of this program in the United States would result in reduced waiting list time and decreased pretransplant infant mortality without an increase in posttransplant mortality. However, at the present time, OPTN policy allocates ABO-I hearts to infant candidates only after all attempts to place the organ with an ABO-compatible candidate have failed. Therefore, most infants eligible to receive ABO-I organs continue to receive compatible organs (or die on the waiting list). There is no evidence at this time that the policy of allowing listing for an ABO-I organ has led to a fall in infant waiting list mortality in the United States. If ongoing analyses of posttransplant outcomes continue to reveal no difference in survival between ABO-I and ABO-compatible transplants, then current OPTN policy will need to be reviewed to determine if equal preference should be given to candidates listed for ABO-I and ABO-compatible transplants. New OPTN policy also intends to allow ABO-I transplants to be offered to young children between 1 and 2 years of age if they demonstrate absent or a very low titer of the relevant isohemagglutinins.

Retransplantation

As indicated previously, the prevalence of people living with a functioning heart transplant has increased from 15 593 at the end of 1999 to 19 308 at the end of 2007 [Table 11.16]. Therefore, there are more heart recipients who might ultimately be candidates for retransplantation at later times following transplantation when outcomes are better than when retransplantation is performed for acute rejection or early allograft failure (11,12). This trend is indeed shown in the data available. From 1999 to 2008, a time when the number of active candidates waiting for transplant has declined, the percent of active candidates with retransplantation as the primary diagnosis has steadily increased from 2% to 6% (Figure 20) [Table 11.1 a]. The death rate for candidates for retransplantation has varied over the past decade, but for 2008 was 221 deaths per 1000 patient-years [Table 11.3], representing the highest waiting list death rate for any known primary diagnosis category except for candidates with congenital heart disease. This death rate on the waiting list is consistent with the fact that, although the percentage of patients listed with the indication of retransplantation has increased over the last decade, the percent of transplant recipients that are retransplants has been stable (4% in 1999 and in 2008) (Figure 20) [Table 11.4]. Following retransplantation, 3-month, 1-year, 5-year and 10-year unadjusted graft survival remains inferior to that of all transplant recipients (90%, 84%, 65% and 42% for retransplants vs. 93%, 88%, 74% and 55% respectively) [Table 11.10]. The high rate of deaths on the waiting list for candidates for retrans-



Source: 2009 OPTN/SRTR Annual Report, Tables 11.1a. and 11.4

Figure 20: Heart candidates and heart recipients with prior heart/heart-lung transplant.

plantation is concerning. However, the outcomes for retransplantation remain inferior to those following primary transplantation. Any attempts to allocate more organs to candidates for retransplantation would diminish the overall life-years that could potentially be saved by allocation of those donor hearts to de novo recipients. Ongoing efforts by the heart transplant community to select the best candidates for retransplantation are clearly needed.

Heart-Lung Transplantation

Surgical and medical therapies have improved for many of the diseases that have traditionally been treated with heart-lung transplantation. Examples of this include more sophisticated surgical options for patients with congenital heart disease, a rise in the number of patients with pulmonary arterial hypertension (PAH) treated with lung (single and/or bilateral) transplantation alone, and the larger spectrum of medications (oral, inhaled and intravenous), used for patients with PAH. Because of this, the practice of heart-lung transplantation continues to decrease in the United States and worldwide.

The wait-list characteristics at the end of 2008 demonstrated that a broad spectrum of disease was represented amongst candidates for heart-lung transplantation. Of the 33 candidates actively listed at that time (6 pediatric, 27 adult) [Table 13.1a], the most common diagnoses were the Eisenmenger syndrome spectrum of diseases (55%) and the idiopathic pulmonary arterial hypertension spectrum of diseases (15%). Mixed diseases (such as a combination of coronary artery disease and idiopathic pulmonary fibrosis, or valvular heart disease and COPD) accounted for 14% of candidates.

The number of heart-lung transplant recipients in the United States has declined from 51 in 1999 to 27 in 2008 [Table 13.4]. For those who underwent heart-lung transplant in the years of 2007–2008, (58 total), 33% carried the diagnosis of the Eisenmenger syndrome spectrum of

diseases and 24% the idiopathic pulmonary arterial hypertension spectrum of diseases. Patients with primary cardiac lesions with secondary pulmonary hypertension represented 7% of cases.

Heart–lung recipient survival has generally been less than that of many other forms of transplantation. Approximate adjusted survival rates are 86% at 3 months, 81% at 1 year, 45% at 5 years and 29% at 10 years [Table 13.12]. These rates more closely approximate the survival rates of lung-only transplant recipients than heart-only recipients, suggesting that the biology of survival is dictated more by the presence of bronchiolitis obliterans syndrome than by transplant coronary artery disease. Because of this, a more comprehensive discussion of heart–lung transplantation can be found in the chapter entitled: ‘Lung Transplantation in the United States, 1999–2008’.

Summary

This review of heart transplantation over the past decade has revealed successes (i.e. a decrease in waiting list deaths, especially for Status 1A candidates, and a continued improvement in posttransplant survival), but also presents us with new challenges. The disparities in transplants per million population, deaths on the waiting list and donor heart utilization among OPOs are clearly worthy of further study. In addition, with the increased percentage of patients on VADs at the time of transplant, more detailed data concerning patients on VADs while listed and at transplant are needed to develop a heart allocation policy that goes beyond status to better reflect waiting list mortality and posttransplant benefit. The increased percentage of infants on the waiting list and their high waiting list mortality also challenges us to develop improved methods of bridging infants to transplantation and allocating donor hearts to infants. Only ongoing careful data collection and analysis can help further improve heart allocation policy in such a way as to benefit those most in need while remaining good stewards of a scarce and precious resource, the donor heart.

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Conflict of Interest Statement

The authors declare no conflicts of interest.

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