CHAPTER VI
Heart and Lung Transplantation in the United States, 1996-2005

OVERVIEW

- The number of heart transplants performed and the size of the heart waiting list continued to drop, reaching 2,126 and 1,334, respectively, in 2005.
- Over the last decade, posttransplant graft and patient survival improved, as did the chances for survival while on the heart waiting list.
- There were 3,170 registrants awaiting lung transplantation at the end of 2005, down 18% from 2004.
- The number of deceased donor lung transplants increased by 78% since 1996, reaching 1,407 in 2005 (up 22% from 2004).
- Death rates for both lung candidates and recipients have been dropping, as has the time spent waiting for a lung transplant.
- Heart-lung transplantation has declined to a small (33 procedures in 2005) but important need in the US.

INTRODUCTION

This chapter describes the state of affairs in thoracic organ transplantation in the United States over the last decade. While there have always been differences of opinion regarding organ utilization and distribution, the focus of these last ten years has been toward reducing waiting list deaths, while improving allocation to enhance outcomes. The fruits of the labors of the Organ Procurement and Transplantation Network's (OPTN) Thoracic Committee and advanced analyses by the Scientific Registry of Transplant Recipients (SRTR) have yet to be fully realized, but there are now policies in place that distribute lungs based on need balanced by predicted outcome, and a new heart policy that encourages broader geographic sharing of organs and is predicted to reduce waiting list deaths. The changes brought by these new policies will be watched closely for equity and fairness, with the ongoing intention of maintaining a system that is aimed at patient need. Exciting new, and sometimes preliminary, information is discussed below.

HEART

Heart Waiting List Characteristics

The waiting list characteristics presented here represent potential transplant recipients on the waiting list at the end of each calendar year from 1996 to 2005 (Table VI-1). The total number of patients active on the heart waiting list continued to decline during this time period to an all-time low of 1,334, a 45% reduction since 1996. This reduction was most prominent in transplant candidates with a coronary artery disease classification (a 53% reduction, Figure VI-1) and in the age range of 35-64 (Figure VI-2). The reduced size of the heart waiting list may reflect better outcomes from improvements in medical, interventional, and surgical treatments of coronary disease *[Table 11.1a]*.

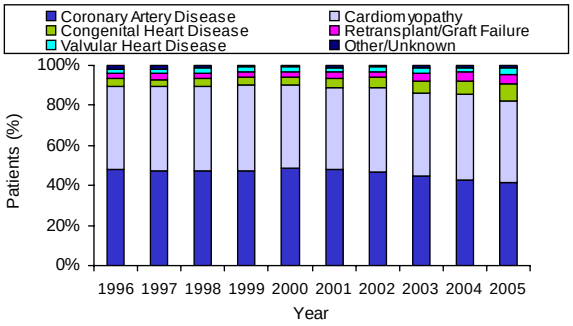
Table VI-1: Active Heart Waiting List Patients *

Year	Patients Active
1996	2436
1997	2414
1998	2525
1999	2478
2000	2421
2001	2257
2002	2055
2003	1809
2004	1590
2005	1334

* Patients listed as active at end of each year.

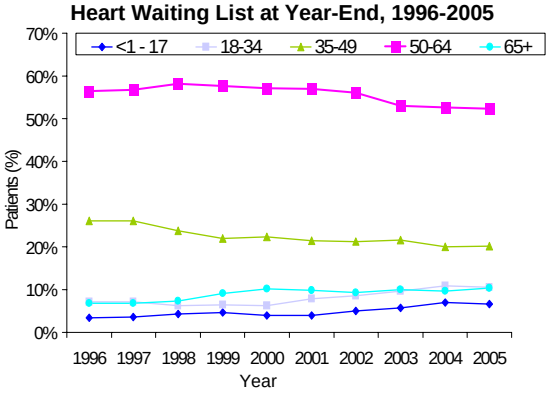
The number of white patients, relative to other ethnicity categories, has seen a 51% reduction since 1996. A much less dramatic decrease of 23% was observed in African Americans (Figure VI-3). The percentage of patients waiting with blood type O has increased by approximately 9% and the percentage of females waiting has increased by approximately 5%. Other characteristics, such as country of residence, have remained relatively unchanged over time (98.9% to 99.9% of patients were U.S. residents in every year since 1996) *[Table 11.1a]*.

Figure VI-1. Primary Diagnoses of Patients Active on the Heart Waiting List at Year-End, 1996-2005



Source: *2006 OPTN/SRTR Annual Report*, Table 11.1a.

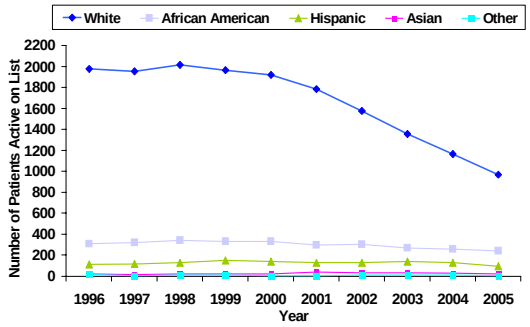
Figure VI-2. Age Distribution of Patients Active on the Heart Waiting List at Year-End, 1996-2005



Source: *2006 OPTN/SRTR Annual Report*, Table 11.1a.

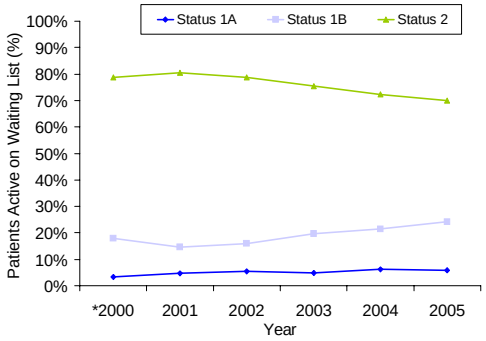
There has been an increasing proportion of Status 1B patients since 2000 (18% in 2000 to 24% in 2005) with a corresponding decrease in the proportion of Status 2 patients listed (79% in 2000 to 70% in 2005). Status 1A has remained generally stable over time (Figure VI-4).

Figure VI-3. Race of Patients Active on the Heart Waiting List at Year-End, 1996-2005



Source: *2006 OPTN/SRTR Annual Report*, Table 11.1a.

Figure VI-4. Status of Patients Active on the Heart Waiting List at Year-End, 2000-2005



*Data prior to 2000 not shown due to change in status categories

Source: *2006 OPTN/SRTR Annual Report*, Table 11.1a.

This indicates a relatively large shift in patients from the more stable Status 2 to Status 1B.

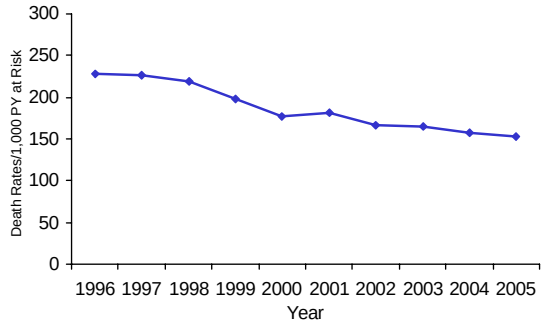
The rules for listing as Status 1A include a high risk of dying within seven days of listing, having a ventricular assist device (VAD) in place (limited to 30 days), or having VAD complications such as infection or being on mechanical ventilatory support. As of January 1, 2005, 26% of patients listed as Status 1A were still listed as Status 1A at the end of 30 days *[Table 11.2b]*. Though patients were to be limited to a maximum of 30 days at Status 1A, at 60 days 12% were still listed as Status 1A and at 90 days there were 10% still listed.

Definitions for each status group are as follows: A Status 1A candidate has either mechanical circulatory support for acute hemodynamic decompensation, support with objective medical evidence of device-related complications, continuous mechanical ventilation, or continuous infusion of intravenous inotropes, in addition to continuous monitoring of left ventricular filling pressures. Additionally, a patient may be listed as Status 1A in the absence of these conditions if the transplant physician submits an application for status to the applicable Regional Review Board for review and the application is subsequently approved. The decision of the Regional Review Board is also reviewed by the OPTN Thoracic Organ Transplantation Committee. A Status 1B candidate has a left and/or right ventricular assist device implanted and/or continuous infusion of intravenous inotropes. A candidate not meeting the conditions for Status 1A or Status 1B may be listed as Status 2.

Deaths On The Heart Waiting List

Overall numbers and death rates in patients awaiting heart transplantation have been declining over the last ten years from a death rate of 227 per 1,000 patient-years at risk in 1996 to 152 in 2005 (Figure VI-5), likely a result of improved medical therapy and mechanical support for patients with advanced heart failure *[Table 11.3]*. This trend was evident across all ethnic, gender,

Figure VI-5. Annual Death Rate of Patients Awaiting Heart Transplantation, per 1,000 Patient-Years at Risk, 1996-2005

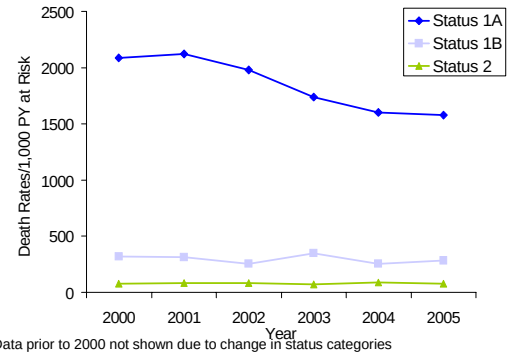


Source: *2006 OPTN/SRTR Annual Report*, Table 11.3.

and blood type groups. It was also evident across all age groups except for ages < 1 year, where the death rate in 2005 was higher than in any of the previous nine years (109 patients in 2005 with 30 deaths).

Death rates have decreased sharply among Status 1A candidates from 2000 to 2005 (2,087 versus 1,580 deaths per 1000 patient-years at risk). Death rates among Status 1B and Status 2 patients have declined less sharply (Figure VI-6).

Figure VI-6. Annual Death Rates per 1,000 Patient-Years on the Heart Waiting List by Status, 2000-2005



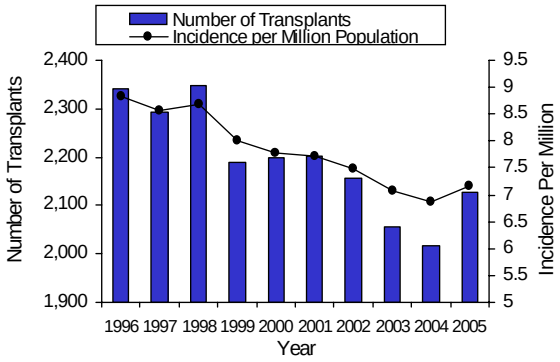
*Data prior to 2000 not shown due to change in status categories

Source: *2006 OPTN/SRTR Annual Report*, Tables 11.3.

Heart Transplant Recipient Characteristics

The overall number of heart transplants has declined by 9% over the last ten years (2,343 performed in 1996 to 2,126 in 2005). There has also been a 19% decrease in the incidence rate of transplant per million U.S. residents (Figure VI-7). Similar to changes in listing

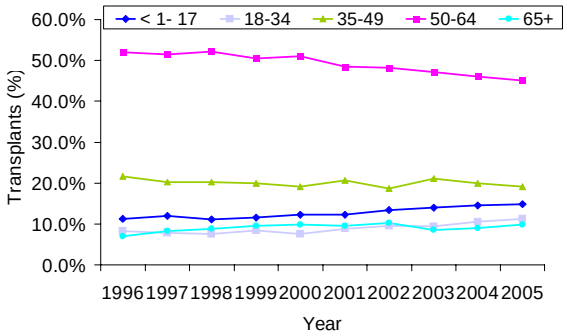
Figure VI-7. Number of Heart Transplants and Incidence of Transplant per Million Population, 1996-2005



Source: *2006 OPTN/SRTR Annual Report*, Tables 11.4 and 11.5.

patterns, these reductions in transplants primarily occur in patients aged 35-64 and in patients with coronary artery disease, likely reflecting improvement in the medical and surgical management of patients with this disease (1-5) *[Table 11.4]*. Patients < 18 years have seen an increase of approximately 20% and 5% for number and incidence per million, respectively *[Table 11.5]*. Patients between the ages of 18 and 34 have seen increases of 26% and 18%, respectively (Figure VI-8).

Figure VI-8. Age of Heart Transplant Recipients, 1996-2005

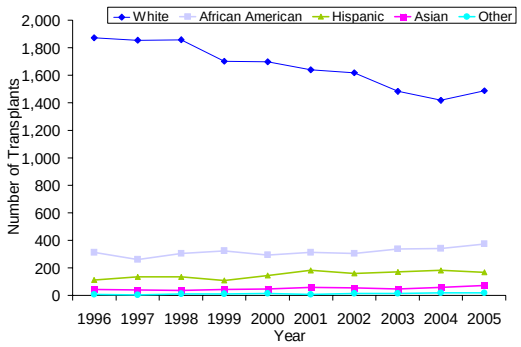


Source: *2006 OPTN/SRTR Annual Report*, Table 11.4.

The number of transplants received by whites has decreased over time, while there has been an increase for the other ethnic categories (Figure VI-9). The proportion of transplants given to males relative to females has

been relatively stable over the last ten years, with males continuing to receive approximately 75% of heart transplants *[Table 11.4]*.

Figure VI-9. Race of Heart Transplant Recipients, 1996-2005



Source: *2006 OPTN/SRTR Annual Report*, Table 11.4.

The waiting list status of heart transplant recipients at the time of transplantation has changed little since the inception of the new classification system in 1999. The percentage of heart transplant recipients who were Status 1A, 1B, and 2 at the time of transplantation has been approximately 40%, 35%, and 25%, respectively *[Table 11.4]*. This is likely to change in the future, with wider geographic sharing of donor hearts for candidates who are Status 1A or 1B. As approved by the OPTN Board of Directors in November 2005 (and as described below) (6), the policy shift towards broader sharing is expected to lead to a decrease in Status 2 transplants in favor of sicker candidates.

Immunosuppression Therapy For Heart Transplantation

The immunosuppression regimen for heart transplantation has continued to evolve over the past decade. Induction therapy was used in 31% of patients in 1996, and has gradually increased to 52% in 2005 *[Table 11.6a]*.

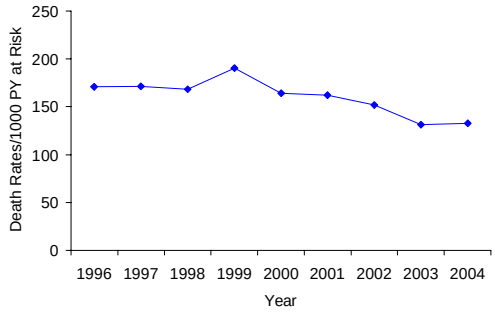
With respect to induction therapy agents, there has been a gradual decline in the use of antilymphocyte antibodies since 1996. Most transplanted patients in 2005 received either rabbit antithymocyte globulin (15%: Thymoglobulin®, SangStat Medical Corp., Fremont, CA), daclizumab (15%: Zenapax®, Roche, Nutley, NJ), and/or basiliximab (14%: Simulect®, Novartis, East Hanover, NJ) [Table 11.6f]. In 2005, triple drug combination therapies were the norm at one year after transplantation. Cyclosporin (CyA) or Tacrolomus (Tac) (Prograf®, Astellas Pharma US, Deerfield, IL) plus Mycophenolate Mofetil/Mycophenolate Sodium (MMF/MPA) (Cellcept®, Roche, Nutley, NJ) plus steroids were the two most common regimens used in patients, respectively (Table VI-2).

A notable trend is the declining number of recipients who needed treatment for rejection episodes during the first year following transplantation (25% in 2004 compared to 40% in 1995) *[Table 11.6i]*. The decline probably reflects the improved efficacy of the newer immunosuppression medications, but also may be due to incremental improvements in the overall care of the donor and recipient. Concurrent trends on the incidence of infection and malignancy deserve study.

Heart Transplant Outcomes

Deaths in the first year after heart transplantation have steadily decreased from 171 deaths per 1000 patient-years at risk in 1996 to 133 in 2004 (Figure VI-10)

Figure VI-10. Annual Death Rate per 1,000 Patient-Years at Risk, for Recipients during First Year after Heart Transplantation, 1996-2004



Source: *2006 OPTN/SRTR Annual Report*, Table 11.7.

[Table 11.7]. Adjusted to the characteristics of the 1995 heart transplant population (adjusted for age, sex, race, and diagnosis of the 1995 population so that comparisons can be made across years), patient survival at three months and one year has also improved from 1996 percentages of 90% and 85% to 2004 percentages of 93% and 88%, respectively *[Tables 11.13]*. Long-term survival has increased at three and five years from 77% and 71%, respectively, in 1996 to 79% and 76% in 2001, the most recent year with adequate posttransplant follow-up. Adjusted graft survival was nearly identical to adjusted patient survival, with adjustments for graft survival based on the age, race, gender and diagnosis characteristics of transplants in 1995.

The prevalence of people living with a functioning heart allograft at the end of each year increased from 12,827

Table VI-2. Immunosuppression Usage Rates in 1995 and 2004 from Discharge to one Year Post- Transplantation for Heart Recipients

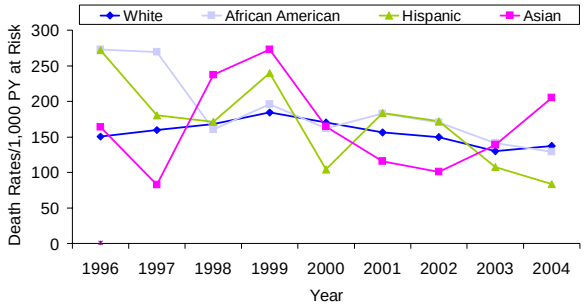
	Year of Transplant	
	1995	**2004**
Number of Transplants	2363	2016
Transplants with Follow-Up Immunosuppression Info	1906 (80.7%)	1607 (79.7%)
Immunosuppressant	***Usage Rates***	
Corticosteroids	90.5%	89.0%
Cyclosporine		
Any in Category	82.2%	48.7%
Cyclosporine	1.6%	0.1%
Sandimmune	42.6%	1.4%
Neoral	37.9%	32.5%
Gengraf	0.0%	14.5%
Eon	0.0%	0.2%
Tacrolimus	10.1%	57.1%
Antimetabolites		
Any in Category	89.2%	94.3%
Mycophenolate Mofetil	11.8%	83.9%
Mycophenolate Sodium	0.0%	0.2%
Azathioprine	76.2%	10.1%
Leflunomide	0.0%	0.0%
Cytoxan	1.2%	0.0%
mTOR Inhibitors		
Any in Category	0.0%	12.8%
Sirolimus	0.0%	12.8%
Everolimus	0.0%	0.1%

Source: *OPTN/SRTR 2006 Annual Report* , Table 11.6g.

in 1996 to 17,329 in 2004 *[Table 11.16]*. These results translate across ethnicity, sex, blood type, primary diagnosis, or waiting list status at the time of transplantation and are a testament to advances in the medical and surgical therapies for end-stage heart disease and posttransplant care.

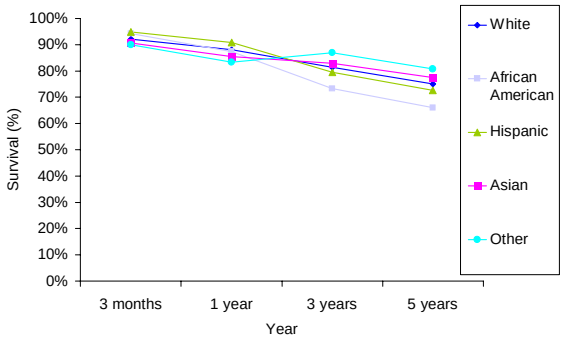
There is variability in how posttransplant death rates have declined since 1996. The downward trajectory of one-year death rates is more marked among African Americans and Hispanics and brings them more into line with one-year death rates of whites (Figure VI-11) *[Table 11.7]*, although African Americans experience somewhat worse survival starting at three-years posttransplant relative to the other ethnicity groups (Figure VI-12). Downward trends in death rates have had more year-to-year variability among the smaller number of Asian transplant recipients. Death rates for females versus males have declined 4% versus 29% since 1996 and women continue to have a slightly worse survival experience over time, with approximately 2% lower survival percentages than males at the same point posttransplant *[Table 11.12]*. Congenital heart disease patients have seen lower posttransplant survival than for coronary artery disease, valvular, and cardiomyopathy patients (Figure VI-13). There is also a greater decline among Status 1A patients compared to the other status categories, since 1999, bringing their posttransplant

Figure VI-11. Annual Death Rate per 1,000 Patient-Years at Risk, for Recipients during First Year after Heart Transplantation, by Race, 1996-2004



Source: *2006 OPTN/SRTR Annual Report*, Table 11.7.

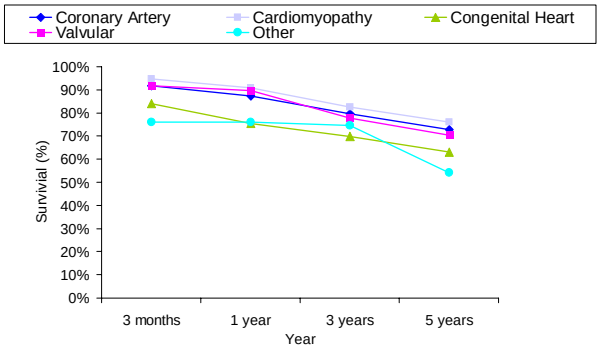
Figure VI-12. Adjusted* Heart Recipient Survival by Race, 1996-2004



* Adjusted to the characteristics of the 3 month/1year cohort (2003-04 transplants)

Source: *2006 OPTN/SRTR Annual Report*, Table 11.12.

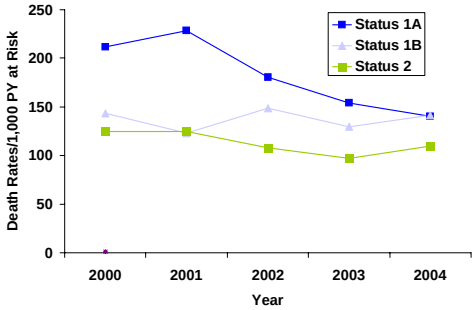
Figure VI-13. Adjusted* Heart Recipient Survival, by Diagnosis, 1996-2004



* Adjusted to the characteristics of the 3 month/1year cohort (2003-04 transplants)

Source: *2006 OPTN/SRTR Annual Report*, Table 11.12.

Figure VI-14. Annual Death Rate per 1,000 Patient-Years at Risk, during First Year After Heart Transplantation, by Status, 2000-2004



*Data prior to 2000 not shown due to change in status categories

Source: *2006 OPTN/SRTR Annual Report*, Table 11.7.

death rates more in line with Status 1B patients (Figure VI-14).

In 2004, annual death rates per 1000 patient-years at risk during the first year after transplantation remained highest for those < 1 year old or those 65 years or older, with death rates of 228 and 198, respectively *[Table 11.7]*. A one-year death rate of 62.9 per 1000 patient-years at risk set a new ten-year low for patients aged 11-17 in 2004. The 2004 death rate during the first year after transplantation was 37% higher in females versus males (165 versus 130, respectively). By diagnosis from highest to lowest, the death rates in 2004 were 266 for congenital heart disease, 216 for valvular heart disease, 140 for coronary heart disease, and 102 for cardiomyopathy.

Heart Allocation Policy Changes

In 1998, in response to public inquiry concerning the equitable allocation of donor organs, the Health Resources and Services Administration of the United States Department of Health and Human Services published a revision to the OPTN Final Rule (7). It was the intent of the Final Rule to not only ensure broad geographic sharing and equitable distribution of organs, but to also minimize discrepancies in waiting times across regions. Implementation of the Final Rule in 2000 required a complete re-evaluation of the nation's organ allocation policies. The responsibility for that re-evaluation ultimately devolved upon the various OPTN committees and subcommittees.

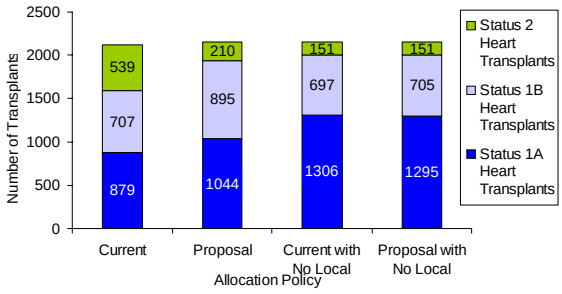
In 2004, the OPTN Thoracic Organ Transplantation Committee began to consider various proposals brought forth by the Scientific Registry of Transplant Recipients (SRTR). The long-term intent of the proposals was to change the allocation system from one based upon waiting time and listing-center-defined medical urgency statuses (1A, 1B, or 2) to an allocation system based upon more data driven estimates of medical urgency and transplant benefit. The concept was not new, having been previously adopted in February 2002 by the liver transplant community and more recently adopted by the lung transplant community, which subsequently implemented their new lung allocation score in May

2005. Draft models are currently being built for heart waiting list and posttransplant patients for use in a new heart allocation score that would replace status 1A, 1B, and 2 designations.

The SRTR also provided data to assess current geographic policies for heart allocation based on status. Traditionally, hearts were allocated locally before being offered out to the region. The natural consequence of this policy was that a Status 2 candidate registered on the local organ procurement organization's (OPO) waiting list would receive a heart prior to a Status 1A or 1B candidate waiting outside of the OPO. Recent studies, however, have demonstrated that transplantation is of marginal early benefit in Status 2 candidates (8).

In view of this information, the OPTN Thoracic Organ Transplantation Committee, in conjunction with the SRTR, assessed the impact of moving Zone A 1A and 1B patients ahead of local Status 2 patients, using the thoracic simulation allocation model (TSAM) to develop an allocation algorithm that would improve the availability of organs for those candidates who are truly the sickest (Figure VI-15). Using data already available,

Figure VI-15. TSAM Results Comparing Heart Transplants from the Four Allocation Policies by Status, 2002

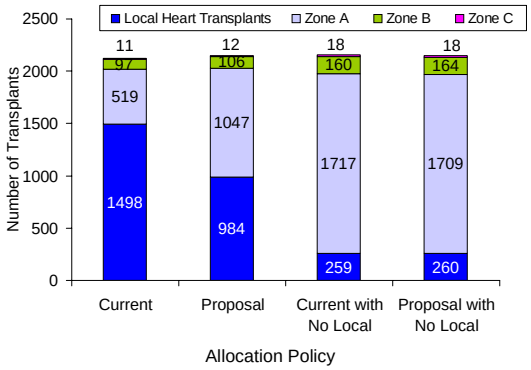


Source: SRTR Analysis, May 2005.

simulation modeling allows one to predict the effect on an allocation policy change on the number of transplants and deaths, before implementing the policy. While some OPTN regions initially opposed the change, expressing concern that the new distribution scheme would disproportionately impact smaller centers situated near larger centers, the Committee nevertheless felt that the global benefit, in terms of lives saved as indicated by TSAM, outweighed the possible risk to the smaller centers.

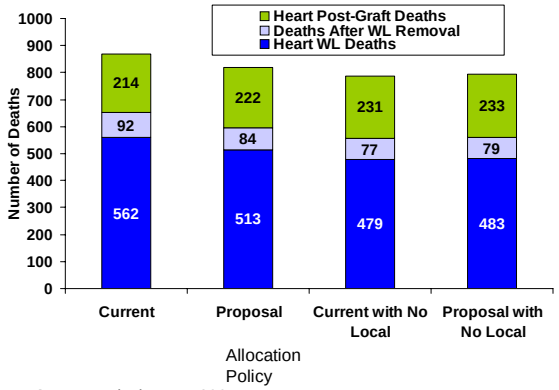
In contrast to the new allocation system for lung transplantation, which uses a combination of risk factors to estimate urgency and the "net benefit" as a result of transplantation, the new heart algorithm which was implemented in July 2006 continues to use the existing status categories to capture urgency and transplant benefit and instead focuses on changes to geographic distribution. In particular, as compared to the prior system, once local 1A and 1B candidates are exhausted, the organ is offered to Zone A (centers within 500 miles), Status 1A and 1B candidates before being offered back to local centers for Status 2 candidates (Figure VI-16). TSAM has repeatedly demonstrated a

Figure VI-16. TSAM Heart Transplant Results From the Four Allocation Policies by Zone, 2002



Source: SRTR Analysis, May 2005.

Figure VI-17. Total Deaths Predicted by TSAM, by Allocation Policy, 2002



Source: SRTR Analysis, May 2005.

g lobal decrease in the number of waiting list deaths and total deaths, and an increase in the number of transplants with this approach (Figures VI-15, VI-17).

Clearly, as TSAM predicts, the number of Status 2 patients undergoing transplantation is expected to decrease significantly. The decrease, however, should be offset by an increase in Status 1A and 1B transplants. This is confirmed by SRTR simulation models. Using the 2002 heart transplant cohort, under the new allocation algorithm Status 2 transplants would have decreased from 539 to 210 (Figure VI-15). In contrast, Status 1A transplants would have increased from 879 to 1044 while Status 1B transplants would have increased

from 707 to 895. In all, total heart waiting list deaths would have decreased from 562 to 513 and total deaths from 868 to 819 (SRTR analysis, May 2005). Admittedly, how this change will affect any individual center is difficult to know. While fewer Status 2 patients will be transplanted at any given center, the number of Status 1A and 1B candidates transplanted should increase as a result of additional imported organs.

For the new scheme to work equitably, programs must be confident that Status 1A (1A(e) in particular) and 1B patients are listed using consistent criteria. This is necessary to ensure that large centers in Zone A do not disproportionately affect neighboring regions by inappropriately listing patients as 1A or 1B who do not technically meet the criteria. The Committee recognized this concern and responded by developing a new listing form which will initially be used for Status 1A(e) patients. It is hoped that via this mechanism the Regional Review Boards will have more information available to make certain that the patient meets the criteria for 1A(e). It is anticipated that in due time additional data will also be collected for status 1A(d) listings as well.

The pediatric heart transplant community expressed concerns that the new allocation algorithm would disproportionately jeopardize Status 2 pediatric candidates. While adult Status 2 patients can be adequately managed medically and may not derive early benefit from transplantation, similar data is not available for the pediatric population due to the smaller numbers. For this reason, the OPTN Thoracic Organ Transplantation Committee elected to treat the pediatric population differently, and continued with the local allocation first policy (Table VI-3).

Other changes of note that occurred over the past twelve months include modifications of UNOS Policy 3.7.3 (Adult Candidate Status). Effective in mid-2006, the requirement that left VAD recipients with device infections be admitted as an inpatient at the listing center in order to remain Status 1(A)(b) has been deleted. (VAD patients with a history of a thromboembolism, device-related complications, and/or malignant arrhythmias will still need to be admitted to the listing center to remain a Status 1(A) candidate.) In addition, heart transplant candidates insured through the Veterans Administration system may now remain at a Veterans Administration facility and stay listed as Status 1A.

Another change to the allocation scheme went into effect July 12, 2006. Now, not only are hearts allocated to Zone A, Status1A and 1B patients before local Status 2, but all alternative allocation systems were also dissolved, in the interest of broader geographic sharing.

Table VI-3. Sequence of Adolescent Heart Allocation

Sequence	Patients
1	Local Status 1 Pediatric Patients
2.	Zone A Status 1A Pediatric Patients
3.	Local Status 1A Adult Patients
4.	Local Status 1B Pediatric Patients
5.	Zone A Status 1B Pediatric Patients
6.	Local Status 1B Adult Patients
7.	Zone A Status 1A Adult Patients
8.	Zone A Status 1B Adult Patients
9.	Local Status 2 Pediatric Patients
10.	Local Status 2 Adult Patients
11.	Zone B Status 1A Pediatric Patients
12.	Zone B Status 1A Adult Patients
13.	Zone B Status 1B Pediatric Patients
14.	Zone B Status 1B Adult Patients
15.	Zone A Status 2 Pediatric Patients
16.	Zone A Status 2 Adult Patients
17.	Zone B Status 2 Pediatric Patients
18.	Zone B Status 2 Adult Patients
19.	Zone C Status 1A Pediatric Patients
20.	Zone C Status 1A Adult Patients
21.	Zone C Status 1B Pediatric Patients
22.	Zone C Status 1B Adult Patients
23.	Zone C Status 2 Pediatric Patients
24.	Zone C Status 2 Adult Patients
25.	Zone D Status 1A Pediatric Patients
26.	Zone D Status 1A Adult Patients
27.	Zone D Status 1B Pediatric Patients
28.	Zone D Status 1B Adult Patients
29.	Zone D Status 2 Pediatric Patients
30.	Zone D Status 2 Adult Patients

Source: OPTN.

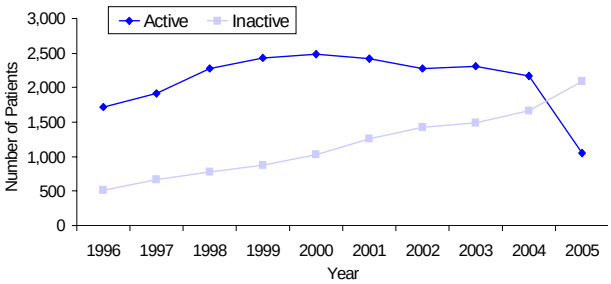
A task force established by the UNOS Board of Directors to oversee the modifications in policy and to evaluate efficacy will follow this change closely.

LUNG

Lung Waiting List Characteristics

At the end of 2005, there were 3,170 registrants awaiting lung transplantation, an 18% drop from the 2004 count of 3,870 [Table 1.3]. An even sharper drop of 51% was seen in active patients on the lung waiting list; from 2,164 in 2004 to 1,053 in 2005 (Figure VI-18) *[Table 12.1a]*. These decreases likely reflect changes in listing practices in response to the implementation in May 2005 of the new lung allocation policy, based on survival benefit and urgency rather than waiting time.

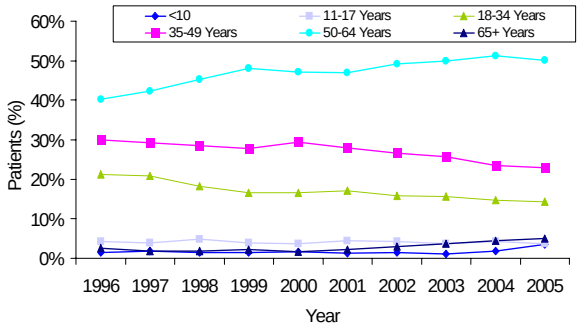
Figure VI-18. Active Versus Inactive Lung Waiting List Patients at Year-End, 1996-2005



Source: *2006 OPTN/SRTR Annual Report,* Tables 1.3 and 12.1a.

The age of active patients on the lung waiting list has changed over the past decade (Figure VI-19), with the percentage of patients over 50 increasing from 43% in 1996 to 55% in 2005, the percentage of patients 18-50 dropping from 51% in 1996 to 37% in 2005, and the percentage of patients 18 years and younger increasing from 6% to 7% *[Table 12.1a]*. Most of these distributional shifts had already taken place over the nine years before implementation of the new lung allocation policy, with only relatively small changes in the distribution between 2004 and 2005. In spite of the small changes in the age distribution between 2004 and 2005, the large change in actual numbers of patients active on the waiting list described above was not consistent over all age groups. The number of patients less than 11 remained fairly stable between 2004 and 2005, while the number of older patients dropped by 52%. This difference is most likely because of the change in lung allocation policy which only applies to patients aged 12 and above; lungs are still allocated on the basis of waiting time to children under age 12.

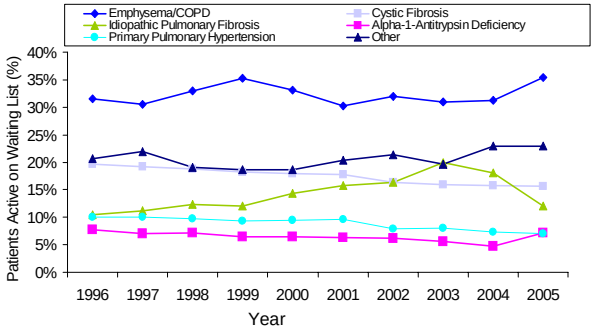
Figure VI-19. Age Distribution of Active Lung Waiting List at Year-End, 1996-2005



Source: *2006 OPTN/SRTR Annual Report,* Table 12.1a.

The diagnosis distribution changed noticeably between 2004 and 2005, with the most dramatic shift in idiopathic pulmonary fibrosis (IPF) patients, who represented 18% of the active lung waiting list at the end of 2004 but only 12% at the end of 2005 (Figure VI-20) *[Table 12.1a]*. This change reflects, in part, a relative increase in the number of IPF transplants under the new policy (28% of lung transplants in 2005 versus 24% in 2004) *[Table 12.4a]*.

Figure VI-20. Primary Diagnoses of Patients Active on the Lung Waiting List, 1996-2005



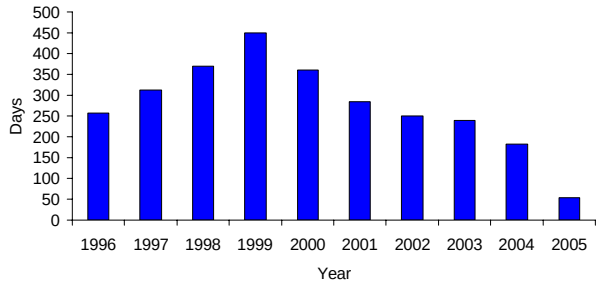
Source: *2006 OPTN/SRTR Annual Report,* Table 12.1a.

The gender and ethnic makeup of the active waiting list changed somewhat between 2004 and 2005. At the end of 2005 the percentage of waiting females, 60%, was the highest observed in ten years, up from 55% at the end of 2004, while the percentage of African American patients dropped from 10% to 8% during that time *[Table 12.1a]*. In 2005, active waiting list patients were most commonly female (60%), white (85%), blood type O (50%), and had not received a previous transplant (97%).

In 2005, relatively fewer patients chose to become inactive if they had been waiting two years or more. In listing two or more years prior, these patients were likely counting on having an organ placement under the old allocation system. The percentage of inactive patients increased in 2005 compared to 2001-2005 *[Table 12.1a and 12.1b]*.

The time by which 25% of newly listed candidates have received a transplant (25th percentile), overall by year of registration, reached a ten-year low of 54 days in 2005 compared to 183 days in 2004 (Figure VI-21), and the

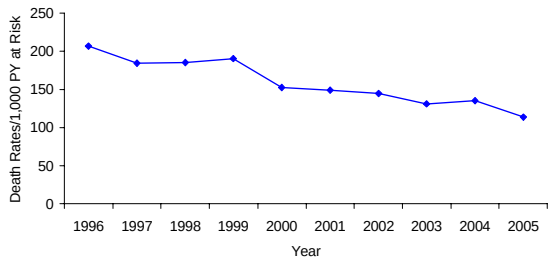
Figure VI-21. Time to Transplant for Lung Registrants, 25th Percentile, 1996-2005



Source: *2006 OPTN/SRTR Annual Report,* Table 12.2.

median time to transplant reached a ten-year low of 202 days in 2005 *[Table 12.2]*. This substantial decrease in time to transplant is a combination of administrative efficiency of lung placement as well as an increase in available organs due to fewer discards under the new system. Time to transplant was shorter in all age groups, ethnic groups, blood type groups, and in both males and females, in 2005 compared to 2004.

Figure VI-22. Annual Death Rate of Patients on the Lung Waiting list, per 1,000 Patient-Years at Risk, 1996-2005



Source: *2006 OPTN/SRTR Annual Report,* Table 12.3.

Deaths on the Lung Waiting List

Death rates among waiting list patients have decreased by 45% over the past decade from 207 per 1,000 patient-years at risk in 1996 to 114 per 1,000 patient-years at risk in 2005 (Figure VI-22) *[Table 12.3]*. Twenty-three percent of this rate decrease was observed between 2004 and 2005.

Although the trend for females to have a slightly lower death rate than males continued in 2005 (112 compared to 117 per 1,000 patient-years at risk), the discrepancy was much smaller in 2005 than in the previous nine years. This change is observed at a time when the percentage of women receiving a lung reached a ten-year low in 2005 at 45% *[Table 12.4a]*.

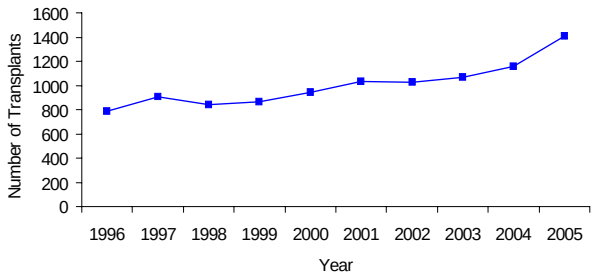
Hispanic patients had much higher death rates than whites, African Americans, or Asians (237 compared to 103, 135, and 135 per 1,000 patient-years at risk, respectively) *[Table 12.3]*. Improvements in death rates between 2004 and 2005 were observed primarily in white patients, despite a similar distribution of transplanted organs by race between 2004 and 2005 and an only slightly shifted distribution of actively listed patients by race between these years *[Tables 12.1a, 12.4a]*. It will be important to watch this dynamic during the next year to see if this pattern evens out.

Patients aged 18-34 years and those 65 years and older had the highest death rates in 2005 (152 and 151 per 1,000 patient-years at risk, respectively), while those aged 35-49 had the lowest death rates in 2005 (87 per 1,000 patient-years at risk) *[Table 12.3]*. The improvements in the death rate between 2004 and 2005 were most evident in those older than 35.

Lung Transplant Recipient Characteristics

The number of deceased donor lung transplants has increased by 78% over the past decade, from 791 in 1996 to 1,407 in 2005 *[Table 12.4a]*. The 2005 number represents a fairly sharp increase from the 1,157 performed in 2004 (Figure VI-23), before implementation of the new lung allocation system and the early stages of the Organ Donation Breakthrough Collaborative. Although all age groups older than 1 year have seen at least some increase in the number of lung transplants over the past decade, the largest increase was seen in patients over the age of 50 (more than doubling between 1996 and 2005). The majority of transplant recipients from 1996 through 2005 continue to be aged 50 to 64 years (58%, Figure VI-24). Changes between 2004 and 2005 were minimal for patients less than 35

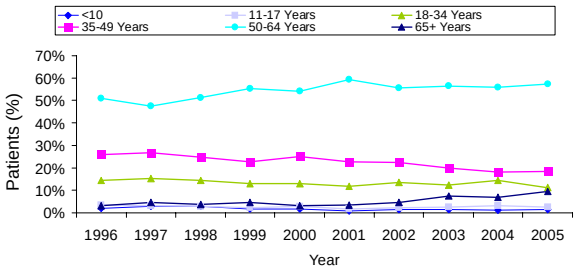
Figure VI-23. Number of Deceased Donor Lung Transplants, 1996-2005



Source: *2006 OPTN/SRTR Annual Report,* Table 12.4.

years old as opposed to the older age groups. The percentage of deceased donor lung transplants performed in females reached a ten-year low in 2005 at 45%, despite a larger percentage of females on both the active and inactive waiting lists *[Tables 12.1b, 12.4a]*. There have been no appreciable changes in the ethnicity (87% white) or blood group type (44% Type O) distribution of recipients of deceased donor lung transplants since 1995.

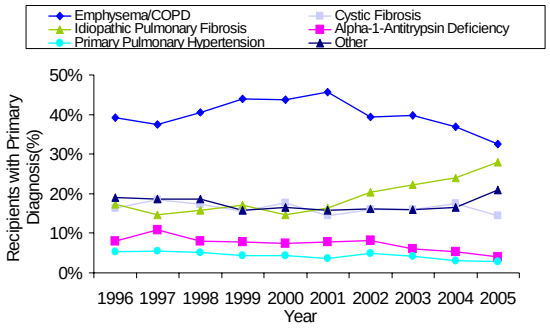
Figure VI-24. Age Distribution of Deceased Donor Lung Transplant Recipients, 1996-2005



Source: *2006 OPTN/SRTR Annual Report,* Table 12.4a.

The number of repeat lung transplants increased 2.2-fold between 2004 and 2005 (from 33 to 74). See Chapter IX in this report for further discussion of repeat transplants. The number of bilateral lung transplants has increased 112% since 1996, to 58% of transplants in 2005 from only 49% in 1996. Emphysema and Chronic Obstructive Pulmonary Disease (COPD) remain the most common diagnoses among lung transplant recipients; 33% of all transplants were performed for these indications. IPF (28%) and cystic fibrosis (CF) (14%) were the next most common diagnoses in 2005. All three of these diagnosis groups have seen either similar or increased numbers of transplants since 2004. That said, the distribution of diagnoses has changed over the last decade and, in particular, since 2004 (Figure VI-25). Comparing

Figure VI-25. Primary Diagnosis of Deceased Donor Lung Transplant Recipients, 1996-2005



Source: *2006 OPTN/SRTR Annual Report,* Table 12.4a.

Figures VI-20 and VI-25 shows that the decrease in the percentage of IPF patients waiting for a lung has been accompanied by an increase in the percentage of transplants performed on these patients. Similarly, the increase in the percentage of patients with COPD and emphysema on the waiting list has been accompanied by a decrease in the percentage of transplants performed in these patients *[Tables 12.1a and 12.4a]*. These observations result from organs being offered to patients with higher lung allocation scores.

Immunosuppression Therapy After Lung Transplantation

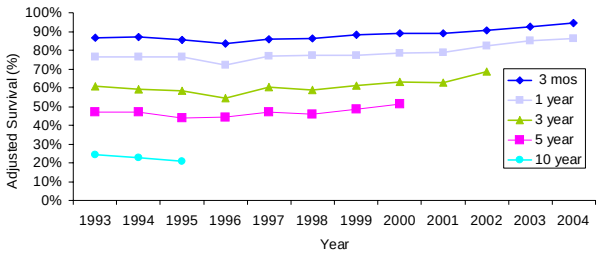
Immunosuppression after lung transplantation has changed significantly since 1995. Induction therapy was used in 43% of all lung transplants performed in 2005, whereas it was used in only 26% of lung transplants in 1996 *[Table 12.6a]*. The induction therapies used most commonly in 2005 were basiliximab (18%) and daclizumab (12%). In 1996, antithymocyte globulin induction therapy was used in 23% of transplants and was by far the most common therapy. In 2005, baseline therapy prior to discharge included corticosteroids (98%), tacrolimus (Prograf®, Astellas Pharma US, Deerfield, IL) (76%), and an antimetabolite, either azathioprine (Imuran®, GlaxoWellcome, New Zealand) (38%) or mycophenolate mofetil (Cellcept®, Roche, Nutley, NJ) (51%). Calcineurin inhibitor use has changed dramatically — from cyclosporine (Neoral® or Sandimmune, Novartis, East Hanover, NJ) (71%) in 1996 to tacrolimus (76%) in 2005 *[Table 12.6e]*. In 2004, maintenance immunosuppression administered between discharge and one year posttransplant was

essentially the same as immunosuppression prior to discharge, except that the use of Sirolimus increased from 0.6% to 9% of lung transplant cases *[Table 12.6g]*. The immunosuppressive agent most commonly used to treat acute rejection within the first year after transplant was corticosteroids, which were used in 94% of acute rejection cases *[Table 12.6i]*.

Lung Transplant Outcomes

The average death rate in the first year after deceased donor lung transplantation has been decreasing steadily over the past ten years, from 366 deaths per 1,000 patient-years at risk in 1996 to 168 deaths per 1,000 patient-years at risk in 2004. Adjusted to the age, race, sex, and diagnosis characteristics of the 2003-2004 deceased donor lung transplant population (three month/one year cohort), patient survival rates for deceased donor lung transplant recipients at three months, one year, three years, and five years were 94%, 85%, 66%, and 51%, respectively *[Table 12.12]*. Adjusted patient survival rates for both short- and long-term follow-up have improved since 1996 (Figure VI-26).

Figure VI-26. Adjusted* Short- and Long-Term Deceased Donor Lung Patient Survival, by Year of Transplant,1993-2004



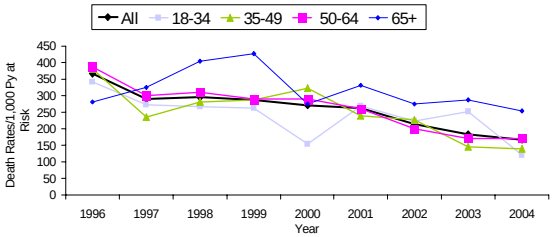
* Adjusted to characteristics of transplants in 1995. Values past 2000 for 5-year, 2002 for 3-year, and 1995 for 10-year survival not determined due to insufficient follow-up.

Source: *2006 OPTN/SRTR Annual Report,* Table 12.13a.

Since 1996, the highest first-year death rate has generally been in the group of recipients aged 65 years and over, who had a rate of 254 deaths per 1,000 patient-years at risk among 2004 recipients (Figure VI-27) *[Table 12.7a]*. The older patients also had a slightly lower five-year survival rate, adjusted for other patient characteristics, when compared to younger recipients *[Table 12.12]*. Death rates in the group aged 35-49 and 50-64 have been generally decreasing over the past ten years (from 381 and 388 for transplants performed in 1996 to 140 and 172 for those performed in 2004, respectively) *[Table 12.7a]*. The trend in the 18-34 year-olds is less clear but may be showing a decrease.

First-year death rates per 1,000 patient-years at risk among ethnic groups in 2004 were lowest for whites at 165, followed by Hispanic/Latinos at 177, and African American at 217; there has been some year-to-year variability in this ordering over the past decade. Asians seem to have better three- and five-year patient survival rates than other race groups but the number of patients in this group is small (83% vs. 61%-74% at three years, and 61% vs. 38%-52% at five years adjusted to the age, sex, and diagnosis characteristics of the 2003-2004 deceased donor lung transplant recipient population) *[Table 12.12]*.

Figure VI-27. Annual Death Rates per 1,000 Patient-Years at Risk, by Age Group, 1996-2004



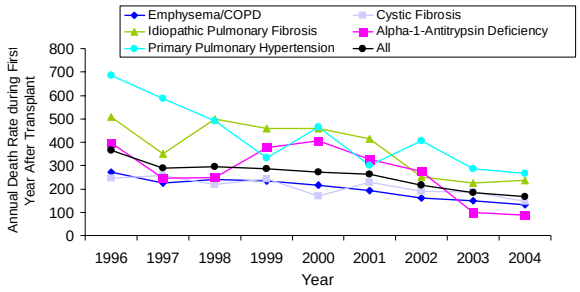
Source: *2006 OPTN/SRTR Annual Report,* Table 12.7a.

The first-year death rates per 1,000 patient-years at risk by sex in 2004 were 10% higher for females at 175 than for males at 160; this was the first time during the past ten years that females had a higher death rate than males *[Table 12.7a]*. Females had an approximate 1-2 percentage point disadvantage in terms of survival at three months, one year, three years, and five years *[Table 12.12]*.

Lung transplant recipients who had received a previous transplant had a higher death rate than first-time recipients (427 versus 161 per 1,000 patient-years at risk) and lower unadjusted graft survival at three months, one year, three years, and five years (79%, 59%, 43%, and 23%, respectively) *[Tables 12.7a, 12.10a]*. In addition, recipients who were hospitalized, admitted to an intensive care unit, or on life support had a higher annual death rate in the first year after transplantation (234, 769, and 371 deaths per 1,000 patient-years at risk, respectively). Recipients with an underlying diagnosis of Primary Pulmonary Hypertension (PPH) continued to have the highest death rate in the first year after transplantation (267 per 1,000

patient-years) compared to recipients with other diagnoses. They were followed by recipients with IPF, cystic fibrosis, and emphysema/COPD (235, 146, and 132 per 1,000 patient-years, respectively) (Figure VI-28). This order is repeated when looking at one-year survival adjusted for other patient characteristics (PPH: 77%, IPF: 81%, cystic fibrosis: 85% and emphysema/COPD: 88%), although five-year adjusted survival is more comparable for these diagnosis groups (PPH: 54%, IPF: 48%, cystic fibrosis: 51%, and emphysema/COPD: 52%, adjusted to the age, sex, and diagnosis characteristics of the 2003-2004 deceased donor lung transplant recipient population) *[Table 12.12]*.

Figure VI-28. Annual Death Rates during First Year after Deceased Donor Lung Transplant, by Primary Diagnosis, 1996-2004



Source: *2006 OPTN/SRTR Annual Report,* Table 12.7a.

Centers with a volume greater than 21 transplants per year had a higher five-year graft and patient survival rate (53% and 55%, respectively) than did lower-volume centers (42%-46% and 45%-50%, respectively), where these percentages are not adjusted for varying characteristics of patients in centers *[Table 12.10a and 12.14a]*. Recipients of lungs from donors aged 50-64 had relatively lower unadjusted five-year graft and patient survival rates (44% and 45%, respectively). This was not true for donors aged 65 and above, although the number of accepted organs from this age group is fairly small and may have a bearing on organ quality.

In general, adjusted graft survival rates for the same time intervals and recipient demographics are similar to adjusted patient survival rates. The reason for the similarity in adjusted graft and patient survival rates is that lung retransplantation is fairly uncommon (5% in 2005) so that the two measure nearly the same thing *[Table 12.4a]*. The reason that so few patients receive second lung transplants has historically been that the outcomes are worse than outcomes of first-time transplants and the ability to survive on the waiting list for a second lung was a limiting factor, as well. Long-term survival, not surprisingly, continues to improve and while The International Society of Heart and Lung Transplantation (ISHLT) composite survival at five years is 48%, a review of the SRTR data suggests that survival at five years now approaches 55%.

Refinements in preservation techniques and acute and chronic patient care continue to take place. This is reflected by the fact that the three month, and one-, three-, and five-year survival rates continue to improve. Furthermore, the near universal adoption of low potassium dextran preservation solutions appears to have safely extended cold ischemia times. SRTR data now suggest ischemia times can comfortably be extended to eight hours *[Table 12.7a]*. Furthermore, the interaction between older age and prolonged ischemia time does not appear to have as strong an adverse effect as was once believed, since the death rates with any given donor age have declined as overall death rates have declined *[Table 12.7a]*.

A significant change in clinical practice relates to the use of Donation after Cardiac Death (DCD) lungs. Anecdotal experience in the past encouraged widespread adoption of techniques espoused at the Consensus Conference on Donation after Cardiac Death in Philadelphia, PA, in April 2005. In 2005, the Organ Donation Breakthrough Collaborative may have contributed to an increase in DCD lung utilization. The technique for DCD recovery is critical, requiring bronchoscopic clearance of the subglottic larynx, as well as the tracheal bronchial tree, immediately prior to extubation of the potential DCD donor. The extubation needs to occur in the operating room in order to have a meaningful chance for successful recovery.

Lung Allocation Policy Changes

The wave of change that followed initiation of the new lung allocation system in May 2005 continues to be felt. Overall, the size of the waiting list has decreased dramatically and the ability to get patients transplanted sooner has been enhanced significantly. However, refinements in the lung allocation system will be possible when longitudinal clinical and outcomes measures for transplant candidates become available. Much of the work by the OPTN Thoracic Organ Transplantation Committee continues to focus on such issues.

Patients with emphysema are transplanted less frequently under the new system, perhaps reflecting an inability to adequately estimate progression of disease. For example, $PaCO_2$ is not yet part of the Lung Allocation Score (LAS), whereas high and rising $PaCO_2$ are known to be predictive of a poor outcome without

intervention. Likewise, patients with pulmonary hypertension also tend to have low lung allocation scores and it has been difficult to track the factors that would appropriately increase their scores, as clinical signs of right heart failure progress. At this point, the OPTN Thoracic Committee plans to collect more data at listing and every six months to analyze and to help better predict outcomes.

Perhaps the next most significant policy change during the last year has been the termination of all alternate allocation schemes. Thus, all rules for allocation are national and not focused on smaller areas of distribution. As patient acuity and potential benefit from transplantation becomes clearer under the new lung allocation system, patient needs will likely supersede center specific demographics. Accordingly, regionalization of thoracic organs as a transplant resource may be in the offing. Furthermore, the safe extension of the cold ischemia times to eight hours implies that broader geographic sharing is both ethical and practical.

Overall, it seems that listed patients are now older, sicker, and more often hospitalized compared to previous years. It is not yet clear whether transplants of sicker patients, after shorter waiting times, will negatively affect outcomes. Ethically, however, when the alternative for such patients is death, it is difficult if not impossible to deny them that opportunity. More retransplants are also being done, despite the fact that acute, mid-, and long-term outcomes are significantly compromised for such patients. Whether or not this practice should continue to expand is controversial and is more thoroughly discussed in Chapter IX in this report.

Double lung transplants are also increasing, justified by the fact that after one year, the survival curves begin to separate and show greater benefit for the double lung recipients compared to single lung recipients *[Tables 12.10a, 12.14a]*. However, diagnosis-specific advantages of single versus double transplantation are less well understood and are not addressed in this Annual Report.

The practice of living donor lobar transplantation has decreased markedly. Between fifteen and twenty-nine of such operations were done annually for the last nine years, but in 2005 only one patient received living donor lungs *[Table 12.4b]*. The ability to transplant patients sooner under the new lung allocation system, has most likely reduced the current demand for living donor transplantation.

Survival after transplantation still varies by listing diagnosis. Patients with pulmonary hypertension have the poorest outcomes at three months and one year, while long-term outcomes appear to be comparable to other listing diagnoses *[Tables 12.8, 12.12]*. Transplant outcomes still correlate with center volume and the clearest inflection point remains at twenty-one transplants per year *[Tables 12.10a, 12.14a]*.

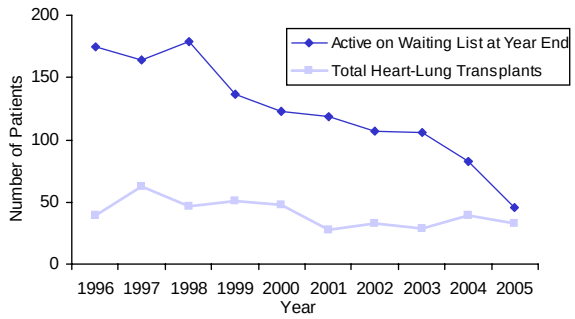
As the criteria for acceptable donor lungs is extended, it appears beneficial to use lungs from donors over 65 years of age. The ideal donor previously had been defined as 55 years of age or younger, but three month, and one-, three-, and five-year survival among recipients who received donor organs from patients over 65 years of age were similar to those receiving organs from younger donors. It should be noted, however, that the number of donors in this age group is small. Long-term survival, not surprisingly, continues to improve and while the ISHLT composite survival at five years is 48%, a review of the SRTR data suggests that survival at five years is comfortably in excess of 50% and may be close to 55%.

Improved knowledge about the safe use of marginal lungs, better preservation techniques, and better communication led to significant increases in the number of transplants performed over the last twelve months. This has been a national trend, but there have also been particular pockets of growth in certain areas of the country including California, Florida, Pennsylvania, and Washington *[Table 12.17]*.

HEART-LUNG

For the seventh consecutive year, the number of patients on the active waiting list for a heart-lung transplant decreased to a ten-year low of 45 patients in 2005 (Figure VI-29) *[Table 13.1a]*. These numbers are very

Figure VI-29. Number of Heart-Lung Patients Active on Waiting List at Year-End and Number of Heart-Lung Transplants, 1996-2005



Source: *2006 OPTN/SRTR Annual Report,* Tables 13.1a and 13.4.

small compared to the nearly 3,000 candidates on the waiting list for heart and over 3,000 candidates on the waiting list for lung. The reason for the decline in the number of active waiting list patients is unclear, but difficulty in obtaining a combined heart-lung block and the relatively poor posttransplant survival, both in the short- and long-term, could be factors, especially combined with the shift toward use of double lung transplants and improved overall survival in lung transplantation.

The 25th percentile of time to transplant decreased to a ten-year low of 100 days in 2005, which is longer than for lung transplant candidates, a 65% decrease from 284 days in 2004 *[Table 13.2]*.

Heart-Lung Recipient Characteristics

There were only 33 heart-lung transplants performed in 2005, a decline from a high of 62 in 1997 *[Table 13.4]*. The most common diagnoses were PPH and congenital heart disease.

Heart-Lung Recipient Outcomes

The SRTR database identifies 57 transplant centers that performed heart-lung transplants at some point between 1996 and 2005. However, 60% of these centers did not perform a combined transplant in 2005 *[Table 13.17]*.

The death rate in the first year posttransplant, reported per 1000 patient-years at risk, was down to a ten-year low at 301 for recipients with transplants in 2004. However, these estimates are based on very few patients *[Table 13.7]*.

On the clinical front, heart-lung replacement continues to have a small but important place in thoracic transplantation in the United States, with thirty-two cases done in 2005 *[Table 1.7]*. While there has been a general decline in the number of registrants for heart-lung transplants *[Tables 1.3 and 1.5]*, the operation will still have a role in the care of patients with combined heart and lung failure and especially vascular diseases, such as Idiopathic Pulmonary Arterial Hypertension (IPAH) and congenital heart diseases with secondary pulmonary hypertension.

As with lung transplantation, heart-lung transplantation has seen an apparent decrease in both the number of registrants and in the time to transplantation *[Tables 1.3, 1.5]*. The causes of this are likely multifactorial, possibly including implementation of the new Lung Allocation System and the Organ Donation Breakthrough Collaborative.

Following in the wakes of both lung and heart transplantation, the management of heart-lung patients has evolved to incorporate newer immunosuppressants. The trend has moved toward broader usage of tacrolimus rather than cyclosporine A, and mycophenolate mofetil instead of azathioprine. These trends become stronger by the first year after transplant *[Tables 1.9 a-c]*. The trend for induction immunosuppression follows that of lung transplantation, with the use of IL-2R inhibitors outweighing the use of anti-lymphocyte and antithymocyte preparations *[Table 13.6a]*, while alemtuzumab (Campath) was used a small minority of the time.

The biggest news in heart-lung transplantation has been the start of the Lung Allocation System in May 2005. In this system, all recipients are categorized by clinical criteria and a priority score for lung allocation is calculated, balancing risk of death without transplant against the predicted outcome with transplantation. As with other multi-organ operations, the heart-lung candidate gets offers as he or she becomes eligible for either organ. The experience has so far been limited, but early mortality figures suggest that current practice has not hurt outcomes. Caution needs to be used in interpreting the data, because the waiting list is very different than in the past, with far fewer patients being listed early, while some who are very ill may now get organ offers despite very short wait times. This may have the tendency to decrease waiting list deaths, while seeming to raise the risk of post-operative mortality. A longer period of observation is warranted to assess the real effect of the LAS on outcomes.

CONCLUSION

Over the last ten years, we have seen major shifts in patient care practices, as well as stunning advances in policy implementation. Heart transplants are performed less frequently than in the past, while lung transplants have never been more numerous. Heart-lung transplants continue to play a small role in total thoracic transplants. Each of these changes has been the result of continuous improvement in management of advanced diseases coupled with thoughtful policy implementation. The overall picture of thoracic transplantation is clear: improvements continue to evolve for the benefit of patients throughout the United States.

REFERENCES

1) Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK, et al. Long-term trends in the incidence of and survival with heart failure. N Engl J Med 2002, 347(18):1397-402.

2) Hunt SA, Baker DW, Chin MH, Cinquegrani MP, Feldman AM, Francis GS, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. J Heart Lung Transplant 2002, 21(2):189-203.

3) Stevenson LW, Miller LW, Desvigne-Nickens P, Ascheim DD, Parides MK, Renlund DG, et al. Left ventricular assist device as destination for patients undergoing intravenous inotropic therapy: a subset analysis from REMATCH (Randomized Evaluation of Mechanical Assistance in Treatment of Chronic Heart Failure). Circulation 2004, 110(8):975-81.

4) Trulock EP, Edwards LB, Taylor DO, Boucek MM, Keck BM, Hertz MI. The Registry of the International Society for Heart and Lung Transplantation: twenty-first official adult lung and heart-lung transplant report--2004. J Heart Lung Transplant 2004, 23(7):804-15.

5) Mahon NG, O'Neill JO, Young JB, Bennett R, Hoercher K, Banbury MK, et al. Contemporary outcomes of outpatients referred for cardiac transplantation evaluation to a tertiary heart failure center: impact of surgical alternatives. J Card Fail 2004, 10(4):273-8.

6) UNOS Board of Directors. Executive Summary of Minutes Nov 17-18, Reston, VA. Available at: http://www.unos.org/SharedContentDocuments/Exec_Sum_of_Minutes_11.05.pdf Accessed August 23, 2006.

7) Federal Register: October 20, 1999 Page 56649-56661 42 CFR Part 121 Available at: http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=1999_register&docid=99-27456-filed. Accessed August 23, 2006.

8) Merion RM, McCullough KP, Murray S, Bustami R, Grover FL. Time-dependent mortality risk of heart transplantation compared with remaining on the waitlist (abstract). J Heart Lung Transplant 2003, 22 (suppl 1): S147.