Lung Retransplantation

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KEYWORDS

• Lung transplantation • Retransplantation • Ethics

Lung transplantation is a therapeutic option for patients with advanced lung disease. Early or late graft failure or airway compromise may lead to significant morbidity and mortality after lung transplantation. Although there are no curative medical or surgical interventions for many of these complications, lung retransplantation is one potential therapy. Retransplantation raises many of the same considerations faced in initial transplantation in terms of indications, selection of candidates, surgical approach, and outcomes, but is complicated by short-term or long-term intensive immunosuppression, infection, and technical issues attributable to the previous transplant. Perhaps the most important (and controversial) aspect of retransplantation is whether allocating a second (or third)[1] lung allograft to one patient while potentially depriving another patient of an initial transplant is ethically justifiable.

Until recently, the issues surrounding lung retransplantation were more theoretical than real because so few were performed. However, changes in the method of lung allocation in the United States have increased the frequency of retransplantation and brought many of these controversies to bear on lung transplant allocation committees and transplant centers. Unfortunately, there is no consensus regarding the medically and ethically appropriate retransplant candidate.

FREQUENCY OF LUNG RETRANSPLANTATION

Four hundred and sixty-six (2.4%) of the 19,524 transplants performed from 2000 to 2008 and reported to the International Society for Heart and Lung Transplantation (ISHLT) Registry were retransplants.[2] There has been a statistically significant increase in the number and percentage of lung transplants that were retransplants performed over the years 2000 to 2008 (both $P \leq .003$) (**Fig. 1**). During the years 2000 to 2004, 40 or fewer retransplants were performed yearly, whereas 60 to 110 were performed yearly between 2005 and 2008. Similarly, less than 2% of all lung transplants in the ISHLT Registry were retransplants between 2000 and 2004, whereas 2% to 4% of transplants were retransplants between 2005 and 2008. Both the mean yearly number of retransplants (77 vs 32) and the mean yearly proportion of lung transplants that were retransplants (2.9% vs 1.7%) were significantly greater for the years 2005 to 2008 than for the years 2000 to 2004 (both $P = .01$).

Lung retransplantation has become more common particularly in the United States.[3] The number of new retransplant candidates and the proportion of new transplant candidates who were retransplant candidates added to the waiting list each year were unchanged over the years 2000 to 2009 (both $P = .10$; **Fig. 2**A). There were no differences in the mean yearly number of patients listed for retransplantation between 2005 and 2009 compared with those listed between 2000 and 2004 (78 vs 69, respectively; $P = .46$). However, there may have been a slight increase in the mean yearly proportion of newly listed patients who were retransplant candidates in 2005 to 2009 compared with 2000 to 2004, but this was not statistically significant (4.1% vs 3.6%, respectively; $P = .08$). Despite the stability in the rates of listing for retransplantation, both the absolute number of retransplants performed and the percentage of transplants that were retransplants significantly increased between 2000

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Clin Chest Med 32 (2011) 367–377
doi:10.1016/j.ccm.2011.02.013

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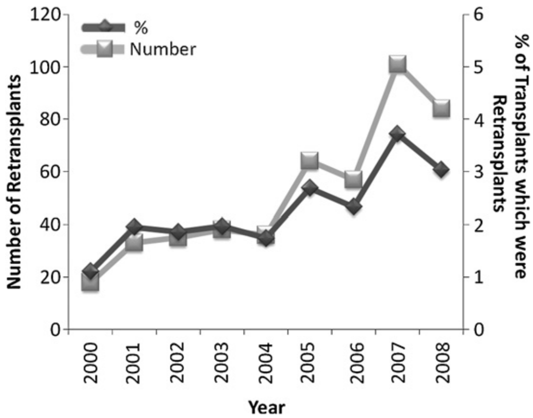

Fig. 1. Adult lung retransplants performed (number and percent of transplants) by year from 2000 to 2008 in the ISHLT Registry (P = .001 and P = .003 for associations between number and percent with time). (*Data from* Christie JD, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: twenty-seventh official adult lung and heart-lung transplant report–2010. J Heart Lung Transplant 2010;29(10):1104–18.)

and 2009 (both $P \leq .003$; see **Fig. 2**B). The mean yearly number of retransplants (62 vs 27) and the mean yearly proportion of lung transplants that were retransplants (4.2% vs 2.6%) were significantly greater for the years 2005 to 2008 than for the years 2000 to 2004 (both P = .01).

These changes in the frequency of lung retransplantation coincided with (and were likely caused by) the introduction of the Lung Allocation Score (LAS) priority system for lung allocation in May 2005 in the United States (see the article by Eberlein and colleagues elsewhere in this issue for further exploration of this topic). Before the LAS system, lung allografts were allocated by time accrued on the list, in addition to geography, body size, and blood type. The LAS system prioritizes patients based on calculations of estimated 1-year survival with and without lung transplantation, favoring those patients with a combination of high net survival benefit (ie, the difference between survival with and without transplantation) and high medical urgency (ie, low estimated survival without transplantation). Because retransplant candidates, specifically with bronchiolitis obliterans syndrome (BOS), had 1-year wait list survival similar to that of idiopathic pulmonary fibrosis, they were included in group D (restrictive lung diseases) in the LAS calculation and are thereby afforded high priority (see the article by Eberlein and colleagues elsewhere in this issue for further exploration of this topic).[4] Retransplant candidates who would not have remained suitable candidates (or alive) long enough with the previous allocation system can receive a lung offer in a timely fashion under the LAS system. Indeed, the median wait time for retransplantation was much shorter for patients listed under the LAS system than for those listed before May 2005 (25 days [interquartile range (IQR), 3–66 days] vs 180 days [IQR, 32–569 days] respectively; $P<.001$).[5] Patients listed for retransplantation had median LAS scores within the upper quintile for patients on the active waiting list from 2006 to 2008,

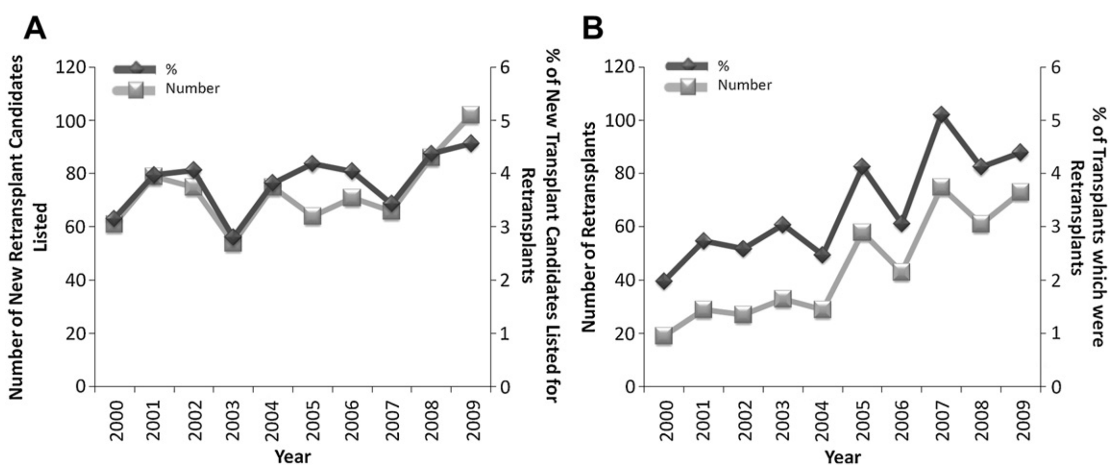

Fig. 2. (*A*) Adult lung retransplantation candidates newly listed (number and percent of candidates) (P = .10 for associations between number and percent with time) and (*B*) adult lung retransplants performed (number and percent of total transplants) by year from 2000 to 2009 in the United States ($P<.001$ and P = .003 for associations between number and percent with time). (*Data from* OPTN as of December 3, 2010. Available at: http://optn.transplant.hrsa.gov.)

explaining the shortened wait times and increase in retransplantation in the United States.[6]

SELECTION OF CANDIDATES

Lung retransplantation may be indicated for lung transplant recipients with severe lung allograft dysfunction which is not amenable to medical or other surgical therapies. The selection criteria for lung retransplantation are similar to those for initial lung transplantation.[7] Absolute contraindications include recent nondermatologic malignancy; untreatable advanced disease of another main organ system; noncurable chronic extrapulmonary infection, including chronic active viral hepatitis B, hepatitis C, and human immunodeficiency virus; significant chest wall/spinal deformity; documented medical nonadherence; untreatable psychiatric condition associated with the inability to cooperate or comply with medical therapy; lack of a consistent or reliable social support system; and active or recent substance addiction. Relative contraindications include older age; unstable clinical status; severely limited functional status; colonization with highly resistant or highly virulent bacteria, fungi, or mycobacteria; obesity; severe or symptomatic osteoporosis; mechanical ventilation; and inadequately treated other medical conditions. Although there are no defined criteria for when lung transplant recipients should be considered for retransplantation, most patients retransplanted in recent years were 1 or more years out from their initial transplant (median 3.1 years; IQR, 1.0–6.5).[5] Key factors that affect outcomes after retransplantation include the indication (in terms of type and timing of allograft failure) and the requirement for mechanical ventilation (see later discussion), so that these factors must figure into the decision to evaluate or list someone for retransplantation. The most common indication for both listing and performance of lung retransplantation in the United States during the past decade was BOS (**Table 1**). A total of 20% of retransplants were performed for primary graft dysfunction (PGD) or acute rejection.

Table 1
Indications for listing and transplanting lung retransplant candidates in the United States between 2000 and 2009

	New Lung Retransplant Candidates Listed (N = 733)		Lung Retransplant Recipients (N = 447)	
BOS	462	63%	292	65%
Primary graft dysfunction	110	15%	77	17%
Acute rejection	28	4%	14	3%
Other	133	18%	64	14%

Data from OPTN as of December 3, 2010. Available at: http://optn.transplant.hrsa.gov/.

TYPE OF PROCEDURE

There are several operative approaches to the retransplant candidate. Patients who have undergone initial bilateral lung transplant may receive either a single or bilateral lung retransplant.[5] Patients who have undergone initial single lung transplantation may undergo ipsilateral or contralateral single lung retransplantation or a bilateral lung retransplantation.

The decision regarding which type of retransplantation to perform is based on a variety of factors. The presence of suppurative infection in the initial allograft (or remaining native lung) warrants explantation and replacement to prevent early infectious complications in the new allograft. Even if not infected, it may still be advantageous to explant the failed allograft that could be a source of ongoing immune stimulation,[8] although most recent retransplantation procedures in the United States leave the allograft behind while having better outcomes than historical retransplant procedures.[5] Technical issues relating to the choice of single lung transplantation for the initial transplant (contralateral chest wall deformity or pleural disease) might dictate the need for ipsilateral single lung retransplantation. Over time, single-single (ipsilateral) retransplant procedures have become less common and bilateral-single retransplant procedures have become more common, likely reflecting the increasing frequency of initial bilateral lung transplantation.[5] Although unadjusted analyses suggest that ipsilateral single lung retransplantation may be associated with a higher risk of death (and contralateral single lung retransplantation associated with a lower risk of death), these findings were not significant predictors of outcome after adjustment for other covariates and were likely confounded by factors, such as indication and timing of retransplantation.[5]

OUTCOMES

The risk of death on the waiting list for patients listed for lung retransplantation in the United States is double or triple that of patients listed for initial lung transplantation.[6] The mean annual death rate on the list for lung retransplant candidates was 295.6 per 1000 person-years for 2005 to 2008, whereas it was 118.2 per 1000 person-years for all lung transplant candidates.

Only a handful of small studies of the risk factors and outcomes in lung retransplantation have been published. A prospective multicenter registry enrolled 230 retransplant recipients from 47 centers between 1985 and 1996.[9–14] Twenty-six centers were located in North America, 20 in Europe, and 1 in Australia. The final publication from this study showed a 1-year survival of 47% and 3-year survival of 33%.[14] A total of 63% of patients were retransplanted for BOS. Patients who were either nonambulatory or dependent on mechanical ventilation had a significantly increased risk of death. Retransplantation performed before 1992 was also associated with a higher mortality compared with retransplant performed after that date. Patients without these risk factors had outcomes similar to those of patients undergoing initial lung transplantation. Although rates of BOS after retransplantation overall were similar to those reported after initial transplantation, those retransplanted less than 2 years after their initial transplant had a significantly higher risk of BOS at 2 years, and those retransplanted for BOS demonstrated a more rapid postretransplant decline in forced expiratory volume in 1 second than those retransplanted for other indications. The identification of retransplant patients with outcomes similar to those of initial transplant recipients was suggested to justify retransplantation as a viable and ethical option for certain lung transplant recipients with failing allografts. The limitations in this study are its voluntary registry design and the historical nature of the data.

Brugiere and colleagues[15] presented 15 patients who underwent lung retransplantation for BOS at their center between 1988 and 2002. The 1-year and 5-year survival was 60% and 45%, respectively, outcomes similar to those of initial single lung transplantation at the investigators' center. The median time between initial transplantation and retransplantation was 31 months (range, 12–39 months). All were clinically stable at the time of retransplantation, although 6 required tracheostomy and mechanical ventilation and 6 were not ambulatory. All patients underwent single lung retransplantation (4 ipsilateral, 9 contralateral, and 2 after initial bilateral lung transplantation). The retained allograft was the source of fatal infection in 4 of the recipients. Such infections related to the allograft always occurred in the presence of suppuration, even though bronchiectasis was minimal or absent at relisting for transplant, leading the investigators to propose explantation of the initial allograft whenever possible during retransplantation.

Schafers and colleagues[16] published a cohort of 14 patients who underwent lung retransplantation at their center from 1987 to 1994. One-year and 2-year survival was 77% and 64%, respectively, which was somewhat lower than initial transplantation at this center. These investigators found that preoperative mechanical ventilation was associated with significantly more days in the intensive care unit (61 days vs 13 days; $P<.05$) as was early retransplantation (<90 days from initial transplant) (72 days vs 16 days; $P<.05$). These factors may also have been associated with higher early mortality. The risk of BOS with retransplantation was also higher than that with initial transplant.

Osaki and colleagues[17] published a cohort of 17 patients who underwent lung retransplantation (2 of whom underwent retransplantation twice). One-year and 5-year survival was 59% and 42%, respectively, outcomes that were significantly worse than those with initial transplant at their center. The 1-year and 5-year survival rates for the patients retransplanted for BOS (N = 12) were 67% and 44%, respectively. The need for mechanical ventilation (or extracorporeal life support) appeared to be associated with an increased risk of death (P = .09); however, the presence of a retained allograft was not (P = .31).

Investigators from the Hannover Thoracic Transplant Program recently published a cohort of 54 consecutive patients who underwent lung retransplantation before January 1, 2004.[18] A total of 37 patients were retransplanted for BOS, 10 for PGD, and 7 for airway complications (5 with severe dehiscence and 2 with airway scarring). Survival in those patients retransplanted for BOS mirrored that of patients undergoing initial transplantation from this center (**Fig. 3**). However, the patients with PGD and airway complications had

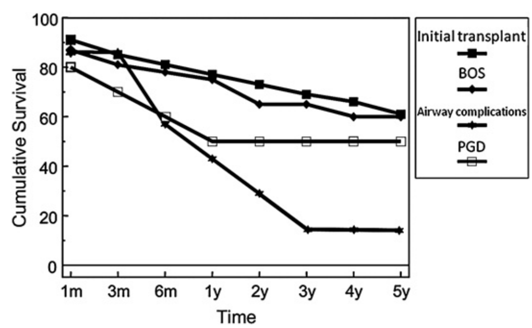

Fig. 3. Survival of lung retransplant recipients (by indication) and initial lung transplant recipients before January 2004 (P = .001 for PGD and airway complications vs BOS and initial transplant). (*Adapted from* Strueber M, Fischer S, Gottlieb J, et al. Long-term outcome after pulmonary retransplantation. J Thorac Cardiovasc Surg 2006;132(2):407–12; with permission.)

a significantly worse survival, leading the investigators to avoid retransplantation for these indications in the latter portion of the study period and, potentially, to confounding by time.

Aigner and colleagues[19] published data from 46 patients who underwent lung retransplantation between 1995 and 2006 in Vienna. They found that patients retransplanted for BOS (N = 19) had 1-year and 5-year survival of 72.5% and 61.3%, respectively, which was significantly better than the survival of patients retransplanted for PGD (N = 23; **Fig. 4**). These estimates did not account for 3 patients who required re-retransplantation. There appeared to be improvement in outcomes over time with retransplant recipients from 2002 to 2006 having better survival than recipients from 1995 to 2001.

The largest retrospective cohort study of lung retransplantation compared modern lung retransplantation to both modern initial lung transplantation and to historical retransplantation in 79 centers in the United States.[5] Patients in the modern retransplant cohort received a first lung retransplantation between January 2001 and May 2006 (N = 205; **Table 2**). Patients who underwent initial lung transplant during this time period were included in the modern initial transplant cohort (N = 5657). Patients who underwent a first lung retransplant between January 1990 and December 2000 comprised the historical retransplant cohort (N = 184). The modern retransplant cohort was significantly older than the historical retransplant cohort but younger than the modern initial transplant cohort (see **Table 2**). Most of the patients in the 3 cohorts had either chronic obstructive pulmonary disease or diffuse parenchymal lung disease as the indication for initial lung transplantation. These diagnoses were less frequent in the modern retransplant patients than in the initial transplant patients, and pulmonary arterial hypertension and cystic fibrosis/bronchiectasis were more frequent. Hypertension, renal failure, and corticosteroid use were significantly more common in the modern retransplant cohort than in the modern initial transplant cohort, and diabetes mellitus was more common in the modern retransplant cohort than both of the other cohorts.

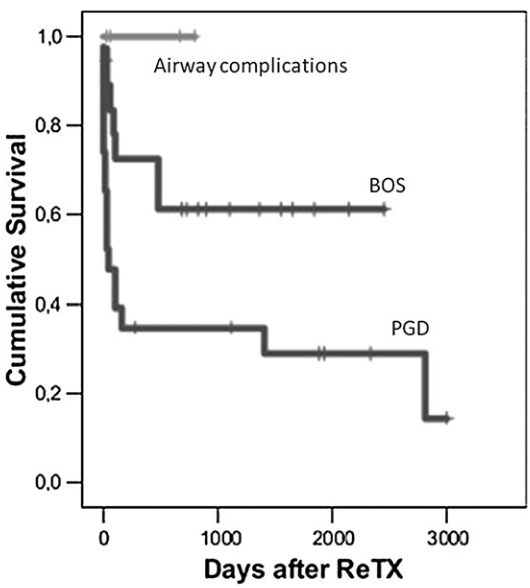

Fig. 4. Survival after lung retransplantation between 1995 and 2006 (P = .02 for PGD vs BOS, other differences were not significant). (*Adapted from* Aigner C, Jaksch P, Taghavi S, et al. Pulmonary retransplantation: is it worth the effort? A long-term analysis of 46 cases. J Heart Lung Transplant 2008;27(1):60–5; with permission.)

Modern and historical retransplant patients were more likely to require mechanical ventilation at the time of transplant than were initial transplant recipients, and more than half of the modern and historical retransplant procedures were performed for BOS. Half of the modern retransplant patients received initial bilateral lung or heart-lung transplantation, and most of these patients went on to receive bilateral lung retransplantation. Modern retransplant patients more often underwent single lung retransplantation after initial bilateral lung transplant than did historical retransplant patients and less frequently underwent ipsilateral single lung retransplantation.

Survival estimates at 1 and 5 years after modern lung retransplantation were 62% and 45%, respectively (**Fig. 5**). Patients undergoing modern lung retransplantation had a significantly lower risk of death after the procedure than that of the historical retransplant cohort, independent of recipient and donor variables, pulmonary diagnosis, and mechanical ventilation at the time of transplant (**Fig. 6**, **Table 3**). On the other hand, patients undergoing modern lung retransplantation still had a 30% higher risk than that of patients undergoing modern initial transplantation (bivariate model, see **Table 3**). Adjustment for recipient and surgical factors attenuated the effect estimates, indicating that differences in these factors explained some, but not all, of the increased risk associated with retransplantation (multivariate models 1 and 2, see **Table 3**). Further adjustment for the presence of renal failure reduced the hazard ratio even further, showing that kidney disease accounted for much of the increased risk of death seen in the retransplantation recipients when compared with initial transplant patients (multivariate model 3, see **Table 3**). Retransplant

Table 2
Recipient and procedure characteristics of modern retransplant recipients (2001–2006), historical retransplant recipients (1990–2000), and modern initial transplant recipients (2001–2006) in the United States

Characteristic	Modern Retransplant (N = 205)	Historical Retransplant (N = 184)	Modern Initial Transplant (N = 5657)
Age, y	43 ± 16	39 ± 17[a]	50 ± 14[b]
Gender, female	109 (53%)	103 (56%)	2721 (48%)
Race/ethnicity			
Non-Hispanic white	182 (89%)	169 (92%)	4935 (87%)
Black	13 (6%)	12 (6%)	414 (7%)
Other	10 (5%)	3 (2%)	308 (5%)
Body mass index, kg/m^2	22 ± 5 (N = 202)	22 ± 6 (N = 172)	24 ± 5[b] (N = 5456)
Initial diagnosis			
Chronic obstructive pulmonary disease	66 (32%)	70 (38%)	2505 (44%)
Diffuse parenchymal lung disease	52 (25%)	32 (17%)	1690 (30%)
Pulmonary arterial hypertension	24 (12%)	28 (15%) [b]	240 (4%) [a]
Cystic fibrosis/bronchiectasis	53 (26%)	33 (18%)	977 (17%)
Other	10 (5%)	21 (11%)	245 (4%)
Diabetes mellitus	74 (36%)	22 (17%)[b] (N = 128)	608 (11%)[b] (N = 5595)
Hypertension	80 (40%) (N = 199)	45 (36%) (N = 125)	993 (18%)[b] (N = 5540)
Renal failure	72 (36%) (N = 200)	56 (30%) (N = 133)	486 (9%)[b] (N = 5583)
Corticosteroid use	151 (79%) (N = 191)	106 (82%) (N = 129)	1881 (35%)[b] (N = 5425)
Mechanical ventilation at time of transplant procedure	40 (20%)	45 (25%)	145 (3%)[b]
Indication for retransplantation			
Bronchiolitis obliterans syndrome	107 (52%)	103 (56%)	—
Primary graft dysfunction	32 (16%)	16 (9%)	—
Acute rejection	7 (3%)	4 (2%)	—
Other or unknown	59 (27%)	61 (33%)	—
Median time from initial transplant, y	3.1 (1.0–6.5)	1.9 (0.5–3.1)[a]	—
Early retransplant (<30 d from initial transplant)	22 (11%)	31 (17%)	—
Procedure type (initial-retransplant)	(N = 201)	(N = 173)	—
Bilateral-bilateral (en bloc included)	67 (33%)	56 (32%)	—
Bilateral-single	41 (20%)	13 (8%)	—
Single-bilateral	31 (15%)	30 (17%) [a]	—
Single-single (ipsilateral)	9 (4%)	33 (19%)	—
Single-single (contralateral)	53 (26%)	41 (24%)	—
Ischemic time, h	5.2 ± 1.9 (N = 182)	5.0 ± 1.8 (N = 157)	4.8 ± 1.7[c] (N = 4934)

Abbreviation: SD, standard deviation.
Data are mean +/– SD, median (interquartile range), or N (%).
[a] *P*<.001 versus modern retransplant.
[b] *P*<.01 versus modern retransplant.
[c] *P*<.05 versus modern retransplant.
Data from Kawut SM, Lederer DJ, Keshavjee S, et al. Outcomes after lung retransplantation in the modern era. Am J Respir Crit Care Med 2008;177(1):114–20; with permission.

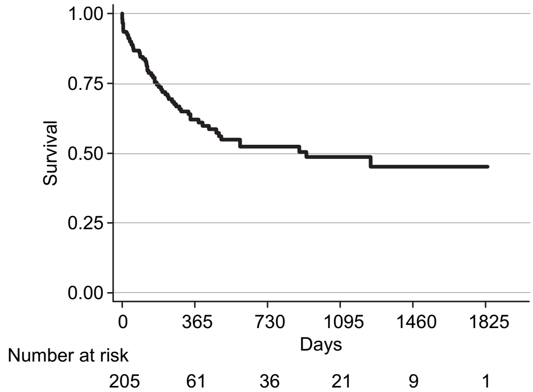

Fig. 5. Kaplan-Meier survival estimate of lung retransplant recipients in the United States from 2001 to 2006. (*From* Kawut SM, Lederer DJ, Keshavjee S, et al. Outcomes after lung retransplantation in the modern era. Am J Respir Crit Care Med 2008;177(1):114–20, Official Journal of the American Thoracic Society, Diane Gern, Publisher; with permission.)

patients had twice the risk of BOS as initial transplant patients (95% confidence interval [CI] 1.4–3.0; $P<.001$).

Although mechanical ventilation at the time of retransplantation and early retransplantation (<30 days from the initial transplant) were both significantly associated with an increased risk of death in unadjusted analyses in the modern retransplant cohort (**Table 4**), only early retransplantation and male donor gender were independently associated with an increased risk of death. The 1-year survival for the 22 patients who underwent early retransplantation was only 31%, whereas it was 66% for the others.

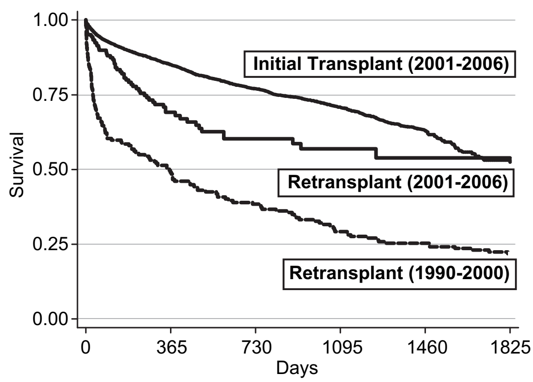

Fig. 6. Survival estimates of modern initial lung transplantation (2001–2006), modern lung retransplantation (2001–2006), and historical lung retransplantation (1990–2000) recipients after adjustment for age (55 years), sex (female), race/ethnicity (non-Hispanic white), procedure type (bilateral), mechanical ventilation (none), and pulmonary diagnosis (chronic obstructive pulmonary disease) ($P<.05$ for all comparisons). (*From* Kawut SM, Lederer DJ, Keshavjee S, et al. Outcomes after lung retransplantation in the modern era. Am J Respir Crit Care Med 2008;177(1):114–20, Official Journal of the American Thoracic Society, Diane Gern, Publisher; with permission.)

This study showed that outcomes after lung retransplantation in the United States have improved over time; however, survival after lung retransplantation was still not as good as that after initial lung transplantation. Based on the multivariate analyses, these differences seemed attributable to a higher prevalence of renal failure and other recipient characteristics. The presence of renal failure in retransplant recipients is likely attributable to long-standing use of calcineurin inhibitors and has been associated with poor outcomes in nonrenal solid-organ transplant recipients.[20] Renal failure is associated with a variety of medical comorbidities that could shorten survival. Alternatively, the presence of renal failure may just serve as a surrogate marker for either the duration and intensity of calcineurin inhibitor-based immunosuppression or the degree of disease of the microcirculation in other organs leading to higher risk after retransplantation.

Early retransplantation independently conferred a high risk for a poor outcome in the modern retransplant cohort. Mechanical ventilation was also associated with an increased risk of death. After adjusting for timing of retransplantation, however, mechanical ventilation was no longer associated with mortality. Therefore, mechanical ventilation may not be a risk factor for patients who are farther out from the initial transplant (eg, with BOS).

In summary, the 1-year and 5-year survival estimates for retransplantation in the modern era are approximately 60% to 80% and 45% to 65%, respectively. Retransplantation for BOS leads to survival estimates in the upper portions of these ranges. Early retransplantation (eg, for PGD) results in poor outcomes, whereas selected patients receiving mechanical ventilation farther out from initial transplant may do well. There is an increased risk of BOS after retransplantation, which may explain the worse outcomes compared with initial transplant, but recipient characteristics and specifically renal failure may also contribute to poor outcomes.

IS RETRANSPLANTATION ETHICALLY JUSTIFIED?

Although the indications, selection criteria, and outcomes for retransplantation are reasonably straightforward, the ethical justification for retransplantation is less so in the setting of scarce organs.

Table 3
Proportional hazards models comparing the risks of death in modern retransplant recipients (2001–2006), historical retransplant recipients (1990–2000), and modern initial transplant recipients (2001–2006) in the United States

	Hazard Ratio	95% CI	*P* value
Modern lung retransplantation vs historical lung retransplantation			
Bivariate	0.7	0.5–0.9	.006
Multivariate[a]	0.7	0.5–0.97	.03
Modern lung retransplantation vs modern initial lung transplantation			
Bivariate	1.3	1.2–1.5	.001
Multivariate model 1[b]	1.2	1.1–1.4	.003
Multivariate model 2[c]	1.2	1.04–1.3	.03
Multivariate model 3[d]	1.1	1.0–1.3	.11

Abbreviation: CI, confidence interval.
[a] Adjusted for recipient age, gender, race/ethnicity, initial diagnosis, single/bilateral retransplantation, indication for retransplantation, ischemic time, mechanical ventilation, donor age, race, and mode of death, early retransplantation, diabetes mellitus, and renal failure.
[b] Adjusted for recipient age, gender, race/ethnicity, body mass index, initial diagnosis, single/bilateral transplantation, ischemic time, and mechanical ventilation.
[c] Model 1 + adjustment for hypertension, diabetes mellitus, corticosteroid use.
[d] Model 2 + adjustment for renal failure.
Data from Kawut SM, Lederer DJ, Keshavjee S, et al. Outcomes after lung retransplantation in the modern era. Am J Respir Crit Care Med 2008;177:114–20.

Because organ donation comes from the deceased and their families and “donated organs belong to the community,”[21,22] the populace views regarding retransplantation are therefore important to consider. A recent systematic review summarized 15 studies eliciting community preferences for organ allocation.[23] Sixty percent or more of respondents preferred allocating organs to initial transplant candidates rather than to retransplant candidates. However, some thought that those who had already received a transplant that failed for medical reasons might have proved themselves able to care for the transplant, warranting priority for another allograft. The vast majority of respondents preferred allocating organs to those with the best chance at survival and improved quality of life with transplant, making these guiding principles for retransplantation.

Several investigators have directly addressed the ethics of solid-organ retransplantation.[24–27] The principle of justice mandates there be equity in distribution of benefits and harms among transplant candidates; however, a rational planner could either discount or favor retransplantation under this principle. For example, it would be rational for an individual (unaware of the future) to prefer a system where the maximal number of people get the opportunity for initial transplantation, rather than one where some undergo retransplantation before others get an initial transplant. In a different scenario, allocating a second organ to a particular patient who has already proven themselves capable of adhering to the complicated medical regimen might increase the chance of success of that transplant and provide greater overall benefit to the population of transplant candidates, still fulfilling the principle of justice in a different way.

Under a just system, transplant candidates each deserve an equal portion of the finite/limited health care pie, all else being equal.[26] One individual should not get a second allograft (or piece) before others have had their first. The problem is that candidates are not perfectly equal. If the pie is considered as the larger construct of health and society, some retransplant candidates may not have had all of the advantages (whether medical, financial, or social) of candidates for initial transplantation. In this scenario, a chance at retransplantation might be “owed” to the transplant recipient, all things considered. These principles of justice would seem to favor lung retransplantation in certain instances, but by themselves are not sufficient to justify retransplant.

Maximizing efficacy (or utilitarianism) refers to the goal of increasing total benefits to transplant candidates overall by targeted organ allocation to those most likely to benefit. Utilitarianism would mandate that initial transplantation be prioritized over retransplantation, because retransplant recipients generally demonstrate a worse survival.[28] Even with initial transplantation, patients with some diagnoses (eg, pulmonary hypertension or

Table 4
Association of recipient and donor characteristics with the risk of death in modern lung retransplant recipients (2001–2006) in the United States

Variable	Hazard Ratio	95% CI	*P* value
Bivariate models			
Recipient			
Age (per 10-y increment)	0.9	0.8–1.1	.45
Male gender	1.4	0.8–2.2	.23
Race/ethnicity: others vs non-Hispanic white	1.6	0.8–3.2	.21
Body mass index (per 5-unit increment)	1.0	0.9–1.0	.92
Initial diagnosis (vs chronic obstructive pulmonary disease)			
Diffuse parenchymal lung disease	1.5	0.7–2.8	.27
Cystic fibrosis/Bronchiectasis	1.3	0.7–2.5	.43
Pulmonary arterial hypertension	1.2	0.6–2.5	.67
Renal failure	1.3	0.8–2.2	.30
Mechanical ventilation at the time of retransplantation	2.0	1.1–3.4	.02
Indication for retransplantation (vs BOS)			
Primary graft dysfunction	1.1	0.6–2.1	.72
Acute rejection	1.2	0.4–3.8	.81
Other or unknown	0.9	0.5–1.7	.80
Donor			
Age (per 10-y increment)	1.1	0.9–1.3	.26
Male gender	1.7	1.0–3.0	.04
Procedure			
Early retransplant (<30 d from initial transplant)	2.6	1.4–4.9	.003
Procedure type (initial-retransplant) (vs bilateral-bilateral)			
Bilateral-single	0.9	0.4–1.7	.71
Single-bilateral	1.1	0.6–2.2	.74
Single-single (ipsilateral)	2.3	0.9–6.1	.09
Single-single (contralateral)	0.5	0.2–1.0	.05
Ischemic time (per 1-h increment)	1.1	0.9–1.2	.44
Multivariate model			
Early retransplant (<30 d from initial transplant)	2.8	1.5–5.4	.001
Donor male gender	1.9	1.1–3.2	.02

Data from Kawut SM, Lederer DJ, Keshavjee S, et al. Outcomes after lung retransplantation in the modern era. Am J Respir Crit Care Med 2008;177:114–20.

sarcoid) have poorer outcomes than patients with other diagnoses (eg, cystic fibrosis and chronic obstructive pulmonary disease). Full pursuit of a utilitarian approach could dictate that all lung allografts be used for those with the best post-transplant survival (or the maximal net benefit), potentially eliminating patients with certain lung disease diagnoses (or requiring retransplant) from candidacy. This approach of course would appear inequitable and unpalatable for initial transplant, and the lung transplant community has already factored efficacy differences into the allocation system to balance utilitarianism with justice and urgency (eg, the appeal process for severely ill patients with pulmonary hypertension), suggesting that neither the community nor policymakers are fully at ease with a utilitarian priority system that sacrifices egalitarianism.[26] Because retransplantation has similar or better outcomes than initial transplant in certain cases, a utilitarian approach seemingly justifies the allocation of allografts for lung retransplantation in such instances.

Prioritarianism favors the worst off[28,29] and directs the allocation of organs to the sickest first, no matter what the outcomes. This approach is not justifiable for either initial transplant or retransplantation in the setting of scarce allograft resources, as efficacy would be significantly compromised and it only considers the sickest at the current time and neglects others who may progress. Similarly, transplant physicians and surgeons may understandably feel bound to prioritize for retransplantation patients whom they have transplanted and cared for (often for years), appropriately regarding the interests of their own patients as paramount.[30,31] However, it is not only acceptable to prioritize the needs of other patients over ones own patients when considering retransplantation (just as with initial transplantation or other scenarios requiring triage or rescue), but the exceptions are also frequent enough that some have suggested professional guidelines for such situations.[30]

A youngest-first strategy (where organs for retransplantation of a significantly younger individual could be prioritized over the initial transplant of an older individual) might be justifiable, beyond the impact of age on urgency or benefit. Public preference strongly supports the allocation of scarce life-saving interventions to younger individuals.[23,28,32] "Because [all people] age, treating people of different ages differently does not mean that we are treating persons unequally."[28,33] Although possibly viewed as ageism, all 66 year olds were once 25 years old and had they needed a lung retransplantation would have had an advantage extended to them under such a system, therefore providing equal opportunity.

In the United States, urgency and efficacy (in terms of net survival benefit at 1 year) determine priority of lung offers within the constraints of geography, compatible blood type, and body size. The policy of the United Network for Organ Sharing is to enhance the overall availability of allografts, balance medical utility (net benefit to all transplant patients as a group) and justice (equity in distribution of benefits and burdens among transplant patients), provide organ offers within comparable time periods for patients depending on their circumstances, and respect the autonomy of persons.[21] Accordingly, retransplantation would (and should) be prioritized lower than many, but not all, initial transplants, but appears ethically justifiable by the same principles that guide all organ allocation.

A key element to the fair allocation of organs for retransplantation lies in the accuracy of the metric of net benefit used to distribute organs. The LAS system is based on survival at 1 year; whether this is the best measure of benefit is controversial. Also, the LAS system did not derive a prediction model specifically for retransplant candidates because of the small population. Therefore, the LAS scores assigned to retransplant candidates are derived from models based on patients with idiopathic pulmonary fibrosis.[4] If the efficacy of lung retransplantation is overestimated by the model, the recent increase in retransplantation procedures under the LAS could be unjustified and jeopardize the ethical stance of lung allocation for retransplantation. For example, 10% of recent LAS scores for retransplant candidates overestimated posttransplant survival by greater than or equal to 231 days and 10% underestimated survival greater than or equal to 83 days, demonstrating somewhat greater variability than for transplant candidates overall.[6] To maintain the appropriate and ethical prioritization of organs for retransplantation in the United States, there should be focused efforts on refining the net benefit calculus for this group, lest misclassification or a spuriously high or low calculated priority threaten just allocation of lung allografts.

In summary, there is a growing number of lung allografts used for retransplantation and a greater percentage of lung transplants that are retransplantations, even though the absolute numbers remain small. The criteria for retransplantation are similar to those for initial transplant, but the optimal technical approach is not clear. Survival after lung retransplantation has improved over time, although it is still worse than after initial transplant. Retransplantation early after initial transplant continues to pose a prohibitive risk and should be avoided. Retransplant is ethically justified; however, prioritization of lung allografts for both initial transplant and retransplantation needs to be guided by the principles of justice and efficacy and must be based on accurate estimates of net benefit. Future efforts should focus on understanding the mechanisms of the increased risk of BOS and higher mortality after retransplantation, honing the selection of optimal candidates and technical approach, and refining the ethical allocation of organs for this procedure.

ACKNOWLEDGMENTS

The author thanks Scott D. Halpern, MD, PhD, MBE for his insightful comments after review of this manuscript. This work was supported in part by Health Resources and Services Administration contract 234-2005-37011C. The content is the responsibility of the author alone and does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government.

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