An economic evaluation of lung transplantation

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Objective: This study was undertaken to determine the cost per quality-adjusted life-year gained with lung transplantation relative to medical treatment for end-stage lung disease in the United Kingdom.

Methods: Patients on the transplant waiting list were used to represent medical treatment. Four-year national survival data were extrapolated to 15 years by means of parametric techniques. Quality-adjusted life-years were derived by means of utility scores obtained from a cross-section of patients. Resource consumption and costs were based on local and national sources. Costs and benefits were discounted at an annual rate of 6%.

Results: Across a 15-year period lung transplantation yielded mean benefits (relative to medical treatment) of 2.1, 3.3, and 3.6 quality-adjusted life-years for single-lung, double-lung, and heart-lung transplantation, respectively. During the same period the mean cost of medical treatment was estimated at \$73,564, compared with \$176,640, \$180,528, and \$178,387 for single-lung, double-lung, and heart-lung transplantation, respectively. The costs per quality-adjusted life-year gained were \$48,241 for single-lung, \$32,803 for double-lung, and \$29,285 for heart-lung transplantation. Sensitivity analysis found the principal determinants of cost-effectiveness to be quality of life and maintenance costs after transplantation.

Conclusions: Lung transplantation results in survival and quality of life gains but remains expensive, with cost-effectiveness limited by substantial mortality and morbidity and high costs. The cost-effectiveness of lung transplantation can be improved with lowered immunosuppression costs and improvements in quality of life after transplantation.

Assessing the benefits of any transplanted organ is problematic. Because the introduction of transplantation was not preceded by clinical trials, there are no true control groups. Most of the evidence on which the benefits of transplantation are based is relatively soft and can still be questioned.^{1,2} Additionally, various factors limit the reliability of data on costs associated with organ transplantation.³ The paucity of hard data on costs and benefits means that few economic data are available for lung transplantation. Ramsey and colleagues⁴ from Washington, DC, published a pilot study on cost-effectiveness of lung transplantation but stressed the need for a prospective multicenter study. The Dutch Medical Technology Assessment Team⁵ followed up with a detailed prospective economic evaluation of the Dutch lung transplant program, but their study was also a single-

center analysis with small numbers. Our article describes a larger study incorporating data from seven transplantation units. The objectives of our study were to ascertain the costs, benefits, and cost-effectiveness of lung transplantation in the United Kingdom relative to medical treatment for end-stage lung disease.

Methods

Study Design and Definition of Treatment Groups

This analysis was a cost-utility study that was based on lung transplantation practice in the United Kingdom. The analysis compared the three main forms of lung transplantation—single-lung, double-lung (including bilateral single-lung transplantation), and heart-lung transplantation—with medical treatment for end-stage lung disease. The perspective for all analysis and discussion in this work was societal; costs accrued by all health care sectors, not just those borne by the transplanting unit, were considered.

Survival Data

Data from the UK Cardiothoracic Transplant Audit, a national database of transplantation in the United Kingdom,⁶ was used to compute survivals. Comparisons between transplantation and medical treatment were made with methods similar to those described by the Dutch group.^{5,7-9} Patients on the organ waiting list were used as a proxy for control patients without transplantation (medical treatment). These patients contributed to the analysis only as long as they remained on the waiting list. Data from patients who underwent transplantation or were removed from the waiting list were censored at time of transplantation or removal. Patients on the waiting list were assumed to be a single group, regardless of diagnosis and type of transplant required.

Survival was based on transplantation and waiting-list activity in the United Kingdom from April 1995 through March 1999, with follow-up till June 2000.

Utility Data

Utility scores were obtained from a parallel study of health-related quality of life in lung transplantation.¹⁰ In that study we measured health utility in a cross-section of transplant recipients with the EuroQol method.^{11,12} Utility was measured on a scale of 0 to 1.

Cost Data

The main costs of transplantation fall into four categories: pretransplantation costs (including transplant assessment and medical care while on the waiting list), donor screening and acquisition, transplant procedure, and long-term follow-up and maintenance. Sources of resource consumption were identified in each category, and costs were assigned in a disaggregated form (costs were figured separately for events and then total cost was derived). The unit consumptions for principal events such as intensive treatment unit stay, hospital stay, reoperations, intra-aortic balloon pump use, rejection episodes, and infection episodes were obtained from prospectively recorded data held by the UK Cardiothoracic Transplant Audit between 1995 and 2000. Several sources, published and unpublished, were used to obtain cost data. These included peer-reviewed literature, accounts departments in transplantation units, the

Department of Health, the regional transplant coordinator's office, and cost data from various health authorities. Best available data were used, with reliance on published or directly measured data wherever possible. Standardized costs for emergency operating theater time, intensive care bed-days, and hospital bed-days were weighted by a factor of 1.3 on the presumption that transplantation is more resource intensive than other types of major surgery. Follow-up costs were based on a model developed by the Papworth unit for modeling posttransplantation costs.¹³

Costs accrued before transplantation and in the first posttransplantation week were assigned to all transplant recipients. Transplant recipients were assumed to have undergone a year of medical treatment before transplantation (on the basis of current median waiting time for lung transplantation in the United Kingdom). The average costs were calculated for the first week then thereafter at increasing intervals to 2 years, after which costs were calculated on a yearly basis. The follow-up costs were based on the proportion of patients surviving to the beginning of a given interval, because costs can only be accrued by patients alive in the given interval. The average cost of an event per transplant recipient for each interval was calculated as follows: cost of event per recipient = proportion of recipients alive at beginning of interval × average cost of event per month for live patient × proportion of survivors experiencing event × interval in months.

Costs beyond 4 years were based on extrapolation of the fourth year's data, allowing for an increasing incidence of obliterative bronchiolitis during 10 years in the transplantation group. It was assumed that the hazard rates for rejection and infection between 36 and 48 months would remain constant in subsequent years.

Costs were computed in 1999 UK pounds sterling (converted to US dollars at the average 1999 rate of £1/\$1.64).

Modeling of Cost-Utility

The cost-utility was modeled across a 15-year period. Costs and benefits were discounted at a rate of 6%. The incremental costs or benefits for single-lung, heart-lung, and double-lung transplantation were calculated as the summation of the differences between the costs or benefits of the respective transplantation group and the medical care group for each time interval. To obtain the quality-adjusted survival, the survival for each interval was multiplied by the utility tariff for that period. The total life-years and quality-adjusted life-years (QALY) gained per procedure could thus be determined by calculating the difference in area under the survival curves. Finally, the cost per life-year or QALY gained was determined by dividing the incremental cost by the incremental benefit of each procedure. Sensitivity analyses were performed to determine the influence of key assumptions.

Statistical Analysis

Data were analyzed with SAS statistical software version 6.12 (SAS Institute, Inc, Cary, NC) for statistical analysis and with Microsoft Excel version 97 (Microsoft Corporation, Redmond, Wash) for spreadsheet-based calculations. Survival analysis was performed with the Kaplan-Meier method, with extrapolation beyond 4 years according to the Weibull method. It was, however, thought unlikely that patients with end-stage lung disease would survive more than 10 years after listing, so all patients in the med-

Figure 1. Survival difference between medical treatment and transplantation calculated as difference in area under curve at discount rate of 6%. *Solid rule*, Medical treatment; *short dashes*, single-lung transplantation (2.0 life-years gained); *long dashes*, double-lung transplantation (2.4 life-years gained); *alternating short and long dashes*, heart-lung transplantation (2.5 life-years gained).

TABLE 1. Survivals with and without transplantation

	1 y	3 y	4 y	10 y	15 y
Waiting list					
Kaplan-Meier (observed)	66%	39%	29%	—	—
Weibull (extrapolated)	67%	37%	29%	5%	0%
Single-lung transplantation					
Kaplan-Meier (observed)	72%	55%	43%	—	—
Weibull (extrapolated)	71%	55%	49%	31%	24%
Double-lung transplantation					
Kaplan-Meier (observed)	69%	59%	51%	—	—
Weibull (extrapolated)	69%	55%	51%	37%	30%
Heart-lung transplantation					
Kaplan-Meier (observed)	69%	57%	54%	—	—
Weibull (extrapolated)	71%	57%	53%	41%	34%

Figure 2. Breakdown of transplantation costs.

TABLE 2. Utility values before and after lung transplantation¹⁰

	0-6 mo	7-18 mo	19-36 mo	>36 mo
Before transplantation	0.31			
Single-lung transplantation	0.69	0.66	0.65	0.61
Double-lung transplantation	0.75	0.83	0.81	0.82
Heart-lung transplantation	0.67	0.85	0.86	0.87

ical treatment arm were assumed to be dead by the end of the 10th year. Day zero for the waiting list analysis was the time of placement on the waiting list.

Results Benefits

Observed survivals with and without transplantation from a 4-year cohort of UK patients (1030 on waiting list and 260 single-lung, 199 double-lung, and 218 heart-lung

TABLE 3. Mean life-years and QALY per patient through 15 years (discount rate of 6%)

	Discounted				Nondiscounted			
	Life-year	QALY	Life-year gained	QALY gained	Life-year	QALY	Life-year gained	QALY gained
Medical treatment	2.7	0.8	—	—	3.1	1	—	—
Single-lung transplantation	4.7	3	2	2.1	6.3	3.9	3.2	3
Double-lung transplantation	5	4.1	2.4	3.3	6.9	5.6	3.8	4.6
Heart-lung transplantation	5.2	4.4	2.5	3.6	7.1	6.1	4.1	5.2

Differences are not exact because of rounding.

TABLE 4. Mean costs incurred through 15 years (discount rate of 6%)

	Medical treatment		Single-lung transplantation		Double-lung transplantation		Heart-lung transplantation	
	UK£	US\$	UK£	US\$	UK£	US\$	UK£	US\$
Before transplantation								
Conventional care			£15,000	\$24,600	£15,000	\$24,600	£15,000	\$24,600
Assessment			£2,910	\$4,772	£2,910	\$4,772	£2,910	\$4,772
Transplantation								
Donor acquisition			£1,444	\$2,369	£1,444	\$2,369	£1,444	\$2,369
Transplant costs			£23,198	\$38,045	£23,198	\$38,045	£23,198	\$38,045
Inpatient follow-up			£4,645	\$7,617	£4,444	\$7,289	£5,225	\$8,569
Posttransplantation follow-up								
Year 1			£15,089	\$24,746	£14,818	\$24,302	£12,565	\$20,607
Year 2			£5,998	\$9,836	£5,824	\$9,551	£5,536	\$9,078
Year 3			£5,550	\$9,102	£5,358	\$8,788	£5,003	\$8,204
Years 4-10			£24,693	\$40,497	£26,263	\$43,072	£26,382	\$43,267
Year 11-15			£9,180	\$15,055	£10,818	\$17,741	£11,509	\$18,875
Medical care alone								
Year 1	£12,888	\$21,136						
Year 2	£9,340	\$15,317						
Year 3	£6,541	\$10,728						
Years 4-11	£16,088	\$26,384						
Total	£44,856	\$73,564	£107,707	\$176,640	£110,078	\$180,528	£108,772	\$178,387

Totals are not exact because of rounding.

TABLE 5. Cost per life-year gained and QALY gained with lung transplantation across the 15-year period

	Benefits discounted				Benefits not discounted			
	Cost per life-year gained		Cost per QALY gained		Cost per life-year gained		Cost per QALY gained	
	UK£	US\$	UK£	US\$	UK£	US\$	UK£	US\$
Single-lung transplantation	£30,991	\$50,825	£29,415	\$48,241	£19,565	\$32,086	£21,077	\$34,567
Double-lung transplantation	£27,678	\$45,393	£20,002	\$32,803	£17,228	\$28,253	£14,076	\$23,084
Heart-lung transplantation	£25,439	\$41,720	£17,856	\$29,285	£15,721	\$25,782	£12,410	\$20,352

recipients) are shown in Table 1, as are the extrapolated survivals to 15 years. On the basis of these data survival curves were derived, from which survival gains across 15 years were computed (Figure 1). Utility values are shown in Table 2. The mean expected survival in the medical arm during the 15-year period was 2.7 years. Relative to this there were incremental benefits of 2.0, 2.4, and 2.5 life-

years gained with single-lung, double-lung, and heart-lung transplantation, respectively. Because the quality of life was better in the single-lung transplantation group, the incremental QALY gain was greater (2.1 for single-lung recipients), with double-lung and heart-lung transplantation giving greater benefit still (3.3 for double-lung recipients and 3.6 for heart-lung recipients). Nondiscounted

Figure 3. Effect of varying utility value and posttransplantation maintenance cost on cost per QALY estimates for single-lung transplantation. Horizontal line defines study cost-utility value of £30,000 per QALY. Diamonds, £250 cost; squares, £500 cost; triangles, £1000 cost.

TABLE 6. Effects of varying selected factors and assumptions on cost per QALY estimates

	Variance in cost per QALY					
	Single-lung transplantation		Double-lung transplantation		Heart-lung transplantation	
	UK£	US\$	UK£	US\$	UK£	US\$
Baseline	£29,415	\$48,241	£20,002	\$32,803	£17,856	\$29,285
Increasing cost of transplant operation from £23,000 to £33,000	+£4,588	+\$7,524	+£3,006	+\$4,930	+£2,739	+\$4,491
If maximal survival without transplant is 5 y	-£115	-\$189	-£117	-\$192	+£117	-\$192
If posttransplantation survivals are 80%, 50%, 35%, and 25% at 1, 5, 10, and 15 y, respectively	-£500	-\$820	-£419	-\$687	+£335	+\$549
Increasing annual cost of medical treatment from £15,000 to £20,000	-£4,657	-\$7,637	-£3,052	-\$5,005	-£2,780	-\$4,559
Increasing mean duration of intensive care admission to 10 d	+£2,921	+\$4,790	+£1,914	+\$3,139	+£1,744	+\$2,860
Increasing cost of treating an infection episode from £2800 to £4000	+£1,993	+\$3,268	+£1,244	+\$2,044	+£804	+\$1,318
Assuming new one-off therapy for obliterative bronchiolitis costing £10,000	+£1,582	+\$2,594	+£983	+\$1,612	+£908	+\$1,489
Assuming monthly maintenance cost increases from £400 to £1200	+£19,415	+\$31,840	+£13,758	+\$22,563	+£12,943	+\$21,226
Varying long-term health utility between 0.4 and 0.9	+£10,892 to -£7,993	+\$17,862 to -\$13,108	+£13,335 to -£1,416	+\$21,869 to -\$2,322	+£13,576 to -£479	+\$22,264 to -\$786

benefits are compared with discounted benefits in Table 3. A substantial proportion of the benefit arising from lung transplantation occurred in the early posttransplantation period. Confining the analysis to benefits in the first 5 years yielded QALY gains of 1.1 for single-lung transplantation, 1.6 for double-lung transplantation, and 1.6 for heart-lung transplantation.

Costs

Summarized costs are shown in Table 4. The mean discounted cumulative costs for 15 years per transplant recipient were £107,707 (\$176,640) for single-lung transplantation, £110,078 (\$180,528) for double-lung transplantation, and £108,772 (\$178,387) for heart-lung transplantation. For the follow-up period, the mean cost per transplant recipient was less than the actual maintenance cost per surviving transplant recipient, because many patients did not survive to incur follow-up costs. The mean cost per transplant fell with each patient death, with patients who died early having less cost implication. For example, although the actual cost incurred by a single-lung transplant recipient in the second year was £9214 (\$15,110), the mean follow-up cost per transplant recipient in the second year was £5,998 (\$9836), because only 70% of transplant recipients survived into the second year. Follow-up costs were higher for heart-lung and double-lung transplantation because of the greater number of survivors (Table 1). Figure 2 shows the proportions contributed by the principal sources of cost in the transplant arm. Of the total cost during the 15-year period, about 40% was related to costs accrued before or at the time of transplantation.

Cost-Utility

Through 15 years, the incremental costs (relative to medical treatment) were £62,851 (\$103,075) for single-lung transplantation, £65,222 (\$106,964) for double-lung transplantation, and £63,916 (\$104,822) for heart-lung transplantation. The costs per life-year and QALY gained derived from these figures are shown in Table 5. Single-lung transplantation was less cost-effective than either double-lung or heart-lung transplantation, with an incremental cost of about £10,000 (\$16,400) per QALY gained.

Sensitivity Analysis

The cost per QALY estimates were relatively stable with adjustment of the survival profile and variation of early posttransplantation assumptions (Table 6). There was, however, considerable variation in cost utility with changes in posttransplantation utility weights and follow-up maintenance costs. With variation in utility weight between 0.5 and 0.9, the cost per QALY shifted by about £10,000 (\$16,400) in all transplantation groups. Figure 3 shows the interaction between utility weights and maintenance costs on cost-utility of single-lung transplantation.

Discussion

This study ventured into a relatively understudied area and is one of few studies that have assessed the cost-effectiveness of lung transplantation. We found that the costs per QALY gained by lung transplantation were £29,415 (\$48,241) for single-lung transplantation, £20,002 (\$32,803) for double-lung transplantation, and £17,856 (\$29,285) for heart-lung transplantation. The cost per QALY estimates were particularly sensitive to changes in utility weightings and follow-up costs after lung transplantation.

Lung transplantation is a relatively new technology. Although the first lung transplants in human beings were reported in 1963,¹⁴ it was not until the 1980s that lung transplantation became a feasible and accepted therapeutic tool.¹⁵ Both cost and effectiveness data are scarce. There is no doubt, however, that lung transplantation is an expensive technology. An early study found the median charge per heart-lung transplant procedure in 1988 to be \$134,881,²⁹ and a later study found a cost per transplant of \$153,921.¹⁶ A search of the medical literature revealed two previous studies on the cost-effectiveness of lung transplantation.^{4,5} A major strength of our study is that, unlike those two studies, our analysis was not dependent on data from a single center but incorporated data from seven centers. These data were therefore more likely to have included the whole spectrum of lung disease and to encompass variations in patient characteristics, patient selection, and clinical practice. A multicenter approach also maximized sample size (whereas our study included survival data from 677 lung transplants, the two earlier studies^{4,5} were based on 28 and 57 transplants, respectively). Our work is also unique in evaluating the cost-effectiveness of single-lung, double-lung, and heart-lung transplantation separately, rather than as a single group.

Some limitations were necessarily imposed by the data and techniques used. First, the use of patients on the waiting list as a proxy for medical treatment and the assumption that all these patients are similar both create limitations.¹⁷ Unfortunately, suitable control patients are lacking, so patients on the waiting list remain the group most representative of medical treatment. Second, our analysis relied largely on extrapolation of data. Parametric extrapolation may give a realistic survival profile by allowing gradual reduction in the hazard rate (patients are increasingly likely to survive longer after having survived to a given period), it does not allow for subsequent increases in hazard, for example, malignancy and other late complications. An implicit assumption is that the utility and cost values in the final epoch measured would persist in the extrapolated study period. Third, indirect costs were not considered in this study. Because lung disease is a source of major disability, there are clear arguments for inclusion of indirect costs, as was done in the Dutch study.⁷ Indirect costs, however, are based on the premise that individuals and their relatives

return to their productive capacity when the disease has been relieved,¹⁸ and there is evidence that many patients do not return to work after transplantation.¹⁹⁻²² It would therefore be a flaw to include costs that assumed restoration of productivity after transplantation without some adjustment for the actual level of productivity. Fourth, we have considered all patients with lung failure to be a homogeneous group. In reality, they comprise a heterogeneous group, and costs and benefits (and thus cost-effectiveness) differ with diagnostic group, operative risk, and other factors. Small numbers, however, prevented any meaningful subgroup analysis. Finally, the difficulty in obtaining reliable UK cost data meant that costs were not assigned from a single source or with a single method. Studies on cost-effectiveness of lung transplantation should be viewed in the context of the relative infancy and continuing evolution of lung transplantation, the heterogeneity of patient groups, the lack of long-term efficacy and cost data, the absence of randomized trial data, and the infancy of cost-utility work in the area.

This study suggests that lung transplantation does result in only a small prolongation in life expectancy. Although the survival gain in this study (from 2.0 to 2.5 years for 15 years) was less than that found in the Dutch study,⁹ which yielded a gain of 4.4 years, that study differed in that lifetime benefits were considered. Additionally, although the survival among patients on the Dutch waiting list^{5,8} was similar to that of those in the United Kingdom, the survivals in the transplantation arm differed, with the Dutch group reporting a 1-year posttransplantation survival of 86%, compared with 71% in the United Kingdom, and thus greater gains in life expectancy. However, the UK survival data are in line with international registry data²³ and are therefore more reflective of the benefit to be expected from lung transplantation in most centers. In contrast, Ramsey and colleagues⁴ found life expectancies to be similar in patients undergoing transplantation and those on the waiting list, which suggests that lung transplantation might not confer a significant survival benefit for all recipients, an assertion later supported by analysis of United Network for Organ Sharing (UNOS) registry data.²⁴

Because of differences in health care systems, costs, and funding, economic data cannot be directly generalized or extrapolated across international boundaries, which is why it is important to perform economic studies in different countries. The cost per QALY found in this study is less than the estimates from the Dutch group (\$71,200)⁹ and from Ramsey and colleagues in the United States (\$176,817).⁴ Economic evaluation of other transplanted organs in the United States and The Netherlands has estimated costs per QALY gained of between \$35,000 and \$40,000 for heart transplantation³⁰ and \$38,000 for liver transplantation.²⁵

Ramsey and colleagues' data⁴ came from a pilot US study and thus represented a small sample from an initial

experience. Because the data were North American, the costs of health care would invariably be higher than in the United Kingdom. The main difference between the Dutch and UK data were in the follow-up costs: monthly costs per patient in the third year were £880 (\$1443) in the United Kingdom and £1255 (\$2058) in the Dutch study. Sensitivity analysis in our study showed that cost-utility was notably sensitive to monthly follow-up values. If the UK monthly maintenance cost rose to £1255, the cost per QALY for single-lung transplantation would be \$77,000. Although the survival profiles in the UK and Dutch cohorts differed, the cost per QALY gained was not sensitive to changing survival profiles. The follow-up costs used in this study were based on data from a single UK unit. It is possible that this unit's management routine differs from management elsewhere. Small variations in management can have major cost implications; for example, Ramsey and colleagues⁴ used an extended regimen of ganciclovir prophylaxis for cytomegalovirus pneumonia, with a single course costing more than \$20,000. Another major difference between the UK and Dutch studies was in pretransplantation costs, which averaged £18,000 and £30,000, respectively. The higher pretransplantation cost in the Netherlands may be due in part to the low acceptance rate (only 10% of all referred patients are accepted for transplantation),²⁶ because substantial costs are accrued by patients who are assessed but not accepted for transplantation. If the pretransplantation costs in this study were the same as in The Netherlands, the cost per QALY gained would increase by about £4000 (\$6560).

Implications

Health care spending on lung transplantation in all countries is currently limited by the availability of donors, and this donor scarcity effectively limits the cost burden of lung transplantation. Although this cost-utility study helps by providing some quantitative economic data on lung transplantation, these data unlikely to have any major implications for general health resource allocation. If xenografts or artificial lungs were to become a clinical reality, however, cost-effectiveness data would assume vital importance, because the limit to the number of transplants performed would depend largely on the funds available to lung transplantation.

The main implications of the data presented in this article are related to decision making within lung transplantation. One major controversy is the choice of procedure: double-lung versus heart-lung transplantation and single-lung versus double-lung transplantation. The data from this study suggest that double-lung and heart-lung transplantation are similar in efficacy and cost-effectiveness, but the same cannot be said for single-lung transplantation. This study adds cost-effectiveness to the arguments favoring the use of double-lung as opposed to single-lung transplanta-

tion. The debate on how best to use the limited supply of donor lungs is not straightforward,^{27,28} however, and is not limited to efficacy and cost-effectiveness. Single-lung transplantation allows more members of society to benefit from transplantation, although at the expense of a poorer quality of life. From an economic viewpoint, the additional societal benefit of single-lung transplantation cannot be neglected and has not been accounted for in this analysis.

Finally, data from economic evaluations are helpful in determining the cost implications of management changes with respect to the overall cost and cost-effectiveness of lung transplantation. For example, one could determine the impact of introducing new management tools (such as a costlier immunosuppressive drug), changes in practice (such as change in listing criteria), or increased availability of donors (such as in xenotransplantation). Incremental cost-effectiveness of several clinical options can thus be determined, providing economic data to guide management decisions.

Lung transplantation is an effective but expensive technology relative to conventional medical treatment. Cost-effectiveness is not an intrinsic characteristic of a technology but depends on how it is applied.¹ It remains desirable to discriminate those patients and circumstances for which single-lung, double-lung, or heart-lung transplantation presents a reasonably cost-effective use of resources, thus allowing efficient use of the limited resources available for both transplantation and general health care provision. As long-term data become available, further studies will define these relationships more precisely.

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Discussion

Dr Bryan F. Meyers (St Louis, Mo). There is clear evidence that because of the high costs of medical care and the infinite capacity of the medical community to spend money on innovative, high-cost, and high-tech medical therapies, we will increasingly be called on to justify the benefits gained for each unit of expen-

diture we make. Work such as this study is essential to the development of our ability to accurately assign relative values to therapies for diverse medical conditions.

Anyanwu and colleagues are to be commended for the meticulous preparation of this article. Its strengths include the involvement of multiple transplant centers, the large number of patients studied, and the care with which the statistical and economic analyses were conducted. To perform such an analysis, one is forced to make multiple assumptions. I personally disagree with many of the assumptions that they made, but much of my disagreement comes from differences in the lung transplantation situation between the United Kingdom and the United States. Our costs for both surgical and medical therapy are much higher, our waiting lists are much longer, and, as a result, our patients are listed earlier in their physiologic decline. As a result, many of the assumptions used for this article would not hold true for our transplant programs. Regardless, this article is a valuable contribution and raises the bar for cost-utility analyses in the field of lung transplantation.

For my first question, can you defend the decision to assign a constant utility or quality of life value to patients on the waiting list? It is clearly acknowledged that pulmonary failure is a progressive process. Patients' conditions deteriorate while they are on the waiting list, and many die or are withdrawn from consideration because of this deterioration. Clearly their measured quality of life must also decline, and your failure to capture this decline diminishes the measured benefit of transplantation.

Second, why did you stratify your analysis on the type of transplant, rather than on other variables that are much more important in determining outcomes? Hosenpud and colleagues in 1998 showed us that when transplantation was compared with medical therapy, lung transplantation decreased mortality risks for patients with cystic fibrosis and idiopathic pulmonary fibrosis, but the mortality risk of lung transplant recipients with emphysema remained higher than that faced by their counterparts on the waiting list for at least the first year after transplantation. Isn't it possible that recipient diagnosis is exerting a hidden influence in your results, because patients with cystic fibrosis, who are younger and who arguably derive the greatest survival and utility benefit, all get double-lung transplants or heart-lung transplants in your system?

Finally, shouldn't these cost-utility estimates be immediately accompanied by some calculation of the error associated with the estimate, such as SD or 95% confidence interval? Your abstract and your article give the strong impression that heart-lung transplantation is most cost-effective, followed by double-lung transplantation and then by single-lung transplantation. This perception is created by reporting only the seemingly precise point estimates of cost per QALY gained. Although your sensitivity analysis is thorough, it is provided late in the article, and it strikes me as analogous to placing a startling headline on the front page of a newspaper and burying the tempering details somewhere in the inner pages. Can we reliably conclude that the cost-utilities for the three procedures are statistically different?

Dr Tom Waddell (*Toronto, Ontario, Canada*). The Cambridge group has just recently published an economic analysis of lung transplantation looking at long-term immunosuppression and the different regimens that are potentially available, and mycophenolate mofetil in particular came out poorly as an expensive option.

What chronic maintenance immunosuppression was used in your economic assumptions?

Dr Abdelghany Mohamed Abdelghany (*Cairo, Egypt*). As for me, it is difficult to compare a life-saving procedure with other medications and other procedures, because lung transplantation is a life-saving procedure for idiopathic pulmonary hypertension in a child. I also want to know how double-lung transplantation is less costly than double-lung transplantation with heart transplantation?

Dr David J. Sugarbaker (*Boston, Mass*). In your extended life table analysis of survival, you predicated the survival after 15 years on the results of the first 4 years. In light of the aggressive nature of bronchiolitis obliterans and the prediction from some groups that if the patient lives long enough, he or she will indeed die of chronic rejection, is that a valid way of calculating extended survival?

Dr Anyanwu. I'll start with the last question. It has to do with extrapolation. As I said, that is a deficiency of any economic study. Bronchiolitis obliterans is not the only thing that can come into play. There is also the issue of neoplasia. The assumption is that the hazards that persist in the first 4 years will continue to decline at the same rate. Unfortunately, every economic study has to make assumptions, and there is no way around this until we have definitive, reliable long-term data. So we had no other way other than to make that extrapolation, but the observation is valid.

With respect to the issue of transplanting two lungs as opposed to one as more cost-effective, I think there are enough data. For example, data from Bavaria and colleagues* and a lot of other workers suggest that transplanting two lungs is physiologically more beneficial than transplanting one lung, and certainly in the United Kingdom we have found the same to be the case in terms of both survival and quality of life.

As regards comparing a life-saving procedure with other procedures, whether we like it or not, we live in the real world. To you spending, say, £1 million to save a life might seem to be the right thing to do; somebody with arthritis might rather have £50,000 pounds spent for a hip replacement. We live in the real world and compete for resources, not only with health care sectors but with non-health care sectors.

Long-term immunosuppression was based on a cyclosporine-based triple-therapy regimen with azathioprine, and the long-term follow-up costs were based on data from the Cambridge group.¹³

With respect to the assumption of constant utility for patients on the waiting list, several assumptions were made because the numbers are small. We had considered dividing this group into diagnostic subgroups, but this would have led to even smaller numbers, and the resulting estimates would be more unstable. The simplifying assumption was necessary because of the small numbers in our study.

We stratified according to the type of transplant. Because part of the debate in lung transplantation is on the type of transplantation that is preferable: single-lung transplantation, double-lung transplantation, or heart-lung transplantation. Another reason is that because there is much practice variation in the United Kingdom, we thought it would be inappropriate to group all three.

It is true that, for example, patients with cystic fibrosis would benefit more, and this probably contributes to the picture of heart-

*Bavaria JE, Kotloff R, Palevsky H, Rosengard B, Roberts JR, Wahl PM, et al. Bilateral versus single lung transplantation for chronic obstructive pulmonary disease. *J Thorac Cardiovasc Surg*. 1997;113:520-7.

lung transplantation as the most cost-effective, because in the United Kingdom this procedure is used primarily for cystic fibrosis. However, I must say that in the Dutch study, in which they grouped all three transplantation types together, their findings were quite similar to ours. As more data emerge, it would be useful to consider emphysema, pulmonary fibrosis, and cystic fibrosis separately, and this would be something that we would look into.

With respect to imprecision of measurement and error rates, the problem is that a cost-utility estimate is based on two separate statistics, the cost and the utility, which are combined. Although we can, for example, get confidence limits for the costs and for the benefits, it is difficult to combine the two to come up with an error measurement for a cost-utility estimate, and how to do this

remains a matter of disagreement among economists and statisticians. Because of this lack of agreement, we have not done that. As I said, however, with sensitivity analysis the assumptions are fairly robust.

Finally, as regards the other question whether the cost-utilities were statistically different between the groups: I did not in any way suggest that heart-lung and double-lung transplantation are different. I think that they are fairly the same. The fact that there was a difference of \$1000 or \$2000 is neither here nor there. To see the difference with single-lung transplantation does not really need statistical testing, however, because the survival is poorer and the quality of life is also poorer, so by definition the cost would be much higher for each unit of benefit.

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