Intrathoracic organ transplantation in the United Kingdom 1995–99: results from the UK cardiothoracic transplant audit

A C Anyanwu, C A Rogers, A J Murday, and the Steering Group

METHODS
The UK cardiothoracic transplant audit
The UK cardiothoracic transplant audit was established to describe the practice of intrathoracic transplantation in the United Kingdom, provide clinical audit, and, by examining outcomes and process, improve cardiothoracic transplant provision. The audit is overseen by a steering group, which comprises the director of each transplant unit, the director of the Clinical Effectiveness Unit at the Royal College of Surgeons, and a Department of Health representative. This paper concerns the description of current practice of intrathoracic transplantation in the United Kingdom only. Other study endpoints include rejection, infection, early post-surgery complications, serum creatinine, and New York Heart Association (NYHA) functional class.

Study design
The UK cardiothoracic transplant audit is an ongoing multicentre prospective cohort study involving all nine United Kingdom thoracic transplant centres. All patients listed for transplantation and all transplants performed in the United Kingdom since April 1995 are recruited. There are no exclusions. Eligible patients are tracked through the national waiting list and transplant database at the United Kingdom Transplant (UKT). There are four data collection points: time of placement on the waiting list, time of transplant, three months post-transplant, and at the annual anniversary of the transplant until death. Data are collected by locally assigned staff in each of the transplant units and submitted to UKT, which processes the data on behalf of the audit. Rigorous data validation is undertaken and consists of three components: data validation at entry, restricting data to valid responses only; computer screening of the database for suspect and invalid data; and periodic visits to centres for direct comparison between submitted data and patient medical records.

End points
The primary end points for this study are mortality and graft survival. Graft survival (defined as the time to retransplantation or death) and patient survival are virtually the same for United Kingdom thoracic transplants because of a low retransplant rate (less than 2% of all transplants). Other study end points include rejection, infection, early post-surgery complications, serum creatinine, and New York Heart Association (NYHA) functional class.

Analysis cohorts
Between April 1995 and March 1999, 2648 patients were added to the national waiting list for intrathoracic organ transplantation. At the time of this analysis, audit registration data had been returned on 2588 (97.7%)—these patients form the cohort for analyses based on the waiting list and include 1521 heart, 710 lung, and 357 heart-lung listings. For transplant data analysis, transplants performed between April 1995 and March 1999 are considered. Data were available on 99% of transplants performed within this period (1737 of
RESULTS
Activity
Figure 1 shows the trend in transplant activity over the four year period. On average, 32 heart, 15 lung, and eight heart-lung patients were added to the waiting list every month. In contrast, the average numbers of heart, lung, and heart-lung transplants per month were 23, 9, and 4, respectively. There was a fall in the average number of heart transplants per month from 27 in 1995 to 22 in 1998. Numbers of lung and heart-lung transplants were relatively constant over the period. Level of activity (and hence the contribution of each centre to this analysis) varied among the nine transplant units (table 1).

Indications for transplant and patient characteristics
The predominant reasons for requiring a heart transplant were dilated cardiomyopathy (n = 679; 44.7%), ischaemic heart disease (n = 578; 38.1%), and congenital heart disease (n = 94; 6.2%). Idiopathic pulmonary fibrosis (n = 201; 28.6%), emphysema (n = 185; 26.3%), and cystic fibrosis (n = 122; 17.3%) were the principal reasons for listing for lung transplantation. Cystic fibrosis (n = 168; 47.1%), primary pulmonary hypertension (n = 67; 18.8%), and congenital heart disease (n = 53; 14.9%) were the most common reasons for listing for a heart-lung transplant. Heart-lung transplantation was the preferred treatment for these diagnoses, as 58% of the patients with cystic fibrosis and 87% of those with primary pulmonary hypertension who were placed on the national waiting list were listed for a heart-lung transplant. Retransplantation was an infrequent reason for listing for heart transplantation (n = 14; 0.9%), but was more common for lung (n = 26; 3.7%) and heart-lung transplantation (n = 8; 2.2%).

Table 2 shows characteristics of patients placed on the waiting list. Centre variations existed: for example, the frequency of listing of critically ill patients (those receiving inotropes, intra-aortic balloon counterpulsation, or ventricular assist devices for circulatory support) varied from 1% to 21%. The median ages at listing were 50 years for heart transplant, 49 years for lung transplant, and 27 years for heart-lung transplant. The age distribution of heart patients was negatively skewed: although the interquartile range was between 41 and 56 years and the 90th centile was 59 years, the age distribution was negatively skewed: although the interquartile range was between 41 and 56 years and the 90th centile was 59 years, the median age was 17 years because of a substantial paediatric contribution—5% of patients added to the heart waiting list were infants or children below eight years of age. The interquartile range of the lung waiting list was similar to that of heart patients (36 to 54 years). The distribution was negatively skewed: although the interquartile range was between 41 and 56 years and the 90th centile was 59 years, the median age was 17 years because of a substantial paediatric contribution—5% of patients added to the heart waiting list were infants or children below eight years of age. The interquartile range of the lung waiting list was similar to that of heart patients (36 to 54 years). The distribution was negatively skewed: although the interquartile range was between 41 and 56 years and the 90th centile was 59 years, the median age was 17 years because of a substantial paediatric contribution—5% of patients added to the heart waiting list were infants or children below eight years of age. The interquartile range of the lung waiting list was similar to that of heart patients (36 to 54 years).
peak at 50 years reflecting the emphysema population. Paediatrics was a minor component of the lung waiting list (2% below 16 years). Those listed for heart-lung transplantation were younger than for lung transplantation (heart-lung: interquartile range 19 to 39 years, 17% below 16 years). The oldest patients placed on the waiting list were 70 years (heart), 66 years (lung), and 57 years (heart-lung).

### Waiting list outcome

After being placed on the waiting list, patients face one of three competing outcomes: transplantation, death on the waiting list, or removal from the waiting list. The probability of receiving a transplant or dying on the waiting list varies with waiting list, or removal from the waiting list. The probability of death (0.0012, falling to 0.0002 after three days was 133 (115 to 149) for heart, 386 (328 to 496) for lung, and 471 (377 to 577) heart-lung. Figure 2 shows the cumulative mortality rate for patients placed on the waiting list. Using the competing risks method, after three years the waiting list survival after competing risks method, after three years the waiting list survival after transplantation in the UK 451

### Donor characteristics

Male donors provided 59% of transplanted organs. This proportion differed among the three transplant groups: 62% of heart and 59% of lung grafts were from male donors, compared with 43% in the heart-lung group. The median donor age (interquartile range) for the three transplant groups was 31 (21 to 42) years for heart, 36 (25 to 45) years for lung, and 27 (17 to 38) years for heart-lung. The oldest donors were 60 years, 65 years, and 61 years for heart, lung, and heart-lung, respectively. Ninety nine transplants were performed with organs from live donors: 91 “domino” heart and eight lobar lung transplants.

### Status at transplant

The sex and age distributions of transplanted patients were similar to those of the waiting list cohort. The ages of the oldest patients transplanted in this cohort were 71 years (heart), 67 years (lung), and 57 years (heart-lung). The underlying diseases in heart and heart-lung recipients were similar to the waiting list cohort. The lung group differed slightly, with a greater proportion of patients having emphysema (35% of those transplanted, compared with 26% on the waiting list). Not all patients received the organs for which they were listed. Some 18% of patients transplanted from the heart-lung waiting list received lung grafts. A smaller proportion (2%) transplanted from the lung list received heart-lung grafts.

### Outcome after transplantation

Graft survival up to three years post-transplantation is shown in fig 3. The one year graft survival was 80% (95% CI, 77% to 82%) for heart, 68% (63% to 73%) for lung, and 70% (62% to 76%) for heart-lung. The failure rate for all transplants was highest in the first post-transplant month. Causes of early graft loss are shown in table 3. For all organs, the risk of graft failure was greatest in the first week after transplantation (probability of failure per day (hazard function) = 0.01). For heart transplants the risk fell after the second week; patients who survive the second week had a much lower daily probability of death (0.0012, falling to 0.0002 after three days.

### Figure 2

Deaths on the waiting list.
months). The picture was different in the heart-lung and lung group—the hazard function remained high for the first three months (0.003/day at one month), accounting for separation of the lung and heart-lung from the heart survival curves after the second week (fig 3). After three months, the hazard rate fell for all grafts; having survived to three months the probability of failure fell to 0.0003 for hearts and 0.0005 for lungs and heart-lungs.

Heart transplant patients had better functional status as determined by the NYHA class, with 84% in NYHA class I at their 12 and 24 month assessment. In comparison, 62% of lung recipients and 67% of heart-lung recipients were in class I at 12 months, while 62% and 69%, respectively, were in class I at 24 months. Lung and heart-lung transplant recipients therefore had worse outcomes than heart recipients in terms of both quantity and quality of survival.

DISCUSSION
The UK cardiothoracic transplant audit is one of a few multicentre collaborative studies evaluating thoracic transplantation. This study represents an almost complete recruitment of centre collaborative studies evaluating thoracic transplantation. The UK cardiothoracic transplant audit is one of a few multicentre studies recruiting patients from selected voluntary registries, which are largely unvalidated, or list, but also to the probability of surviving the transplant operation, as some patients at high risk of death on the waiting list may also be at high risk of death after transplantation, thereby reducing the survival benefit. Listing of patients with relatively mild disease and those with reasonable prognosis, however, increases the demand–supply mismatch and should be discouraged.

The actuarial waiting list survival serves a useful proxy for what the survival would be for end stage organ failure if there

### Table 3 Causes of early graft failure: cause of death for patients who died in the first 30 post-transplant days

<table>
<thead>
<tr>
<th>Cause of failure</th>
<th>Heart</th>
<th>Lung</th>
<th>Heart-lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure related</td>
<td>7/129 (5%)</td>
<td>4/72 (6%)</td>
<td>3/36 (8%)</td>
</tr>
<tr>
<td>Early graft dysfunction</td>
<td>64/129 (50%)</td>
<td>19/72 (26%)</td>
<td>9/36 (25%)</td>
</tr>
<tr>
<td>Infection</td>
<td>10/129 (8%)</td>
<td>17/72 (23%)</td>
<td>8/36 (22%)</td>
</tr>
<tr>
<td>Acute rejection</td>
<td>11/129 (9%)</td>
<td>9/72 (13%)</td>
<td>4/36 (11%)</td>
</tr>
<tr>
<td>Cardiac failure including</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>14/129 (11%)</td>
<td>8/72 (11%)</td>
<td>2/36 (6%)</td>
</tr>
<tr>
<td>Neurological</td>
<td>3/129 (2%)</td>
<td>2/72 (3%)</td>
<td>2/36 (6%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>5/129 (4%)</td>
<td>1/72 (1%)</td>
<td>0/36 (0%)</td>
</tr>
<tr>
<td>Other</td>
<td>15/129 (12%)</td>
<td>12/72 (17%)</td>
<td>5/36 (14%)</td>
</tr>
</tbody>
</table>
Intrathoracic organ transplantation in the UK

were no transplantation.10–13 Our data suggest that mortality risk for patients placed on the waiting list is not as bad as generally perceived. Actuarial waiting list survival in our cohort is similar to that in North America11 and the Netherlands12 (two year actuarial survival, 55% for cystic fibrosis or interstitial pulmonary fibrosis in the USA and 58% for all lung waiting list patients in the Netherlands). There are suggestions that advances in medical management have improved the survival without transplantation,14 and some patients currently placed on transplant waiting lists may actually have a reasonable (mortality-free) prognosis without transplantation.

**Graft survival**

The observed one year graft survival in our present study was at variance with suggestions that patients should now expect a one year survival of 90% for heart transplantation and 80% for lung and heart-lung transplantation.14–15 Indeed several non-UK centres have reported one year survival figures approaching or exceeding 90% for heart transplantation16–20 and also for lung transplantation.21 The international registry,2 however, reports the one year survival for heart grafts done since 1991 as 80% and for lung grafts done since 1994 as 70%, figures similar to those obtained in this study. An audit of a complete national cohort in Germany has recently reported a one year survival of 71% after heart transplantation.22 The most likely explanation for the difference between validated national databases and published reports is publication bias, as those centres with below average results are unlikely to publish their results. Observational studies are particularly prone to publication bias,23 and as transplantation outcome studies are largely observational, published transplant data will be especially prone to such bias.

**Conclusions**

The optimistic outlook at the beginning of the 1990s24–25 and the improved outcomes reported by several centres are not reflected by results in this validated United Kingdom cohort. The problems of high mortality after transplantation and donor scarcity remain. There continues to be a disparity between the numbers of patients listed and the available donors; indeed the heart donor rates have fallen in the United Kingdom over the four year study period. Almost half the patients listed for lung transplantation will not receive a transplant, and at least a quarter will die within two years of listing, while still waiting for a donor. International registry data also suggest that there has been no significant change in survival outcome of heart transplantation since 1986 and for lung transplantation since 1991.24 Continued efforts to expand the donor pool, minimise morbidity and mortality after transplantation, and identify patients who do benefit from transplantation therefore remain crucial. The predominance of deaths in the immediate postoperative period—largely related to early graft dysfunction, infection, and rejection—point to the need for continued research into optimal preservation, antirejection, and infection prophylaxis strategies.

In the absence of national data, health policy and expectations are based on expert opinion, output from research studies, and publications from selected local and international centres. These may not, however, reflect the experiences in normal hospital settings. National audits are therefore valuable in defining the practice and outcome of interventions and establishing the degree to which research findings and results from pioneer and expert units are replicable in routine practice. We suggest that methods similar to those used in this study should be used to study other diseases and interventions where accurate and generalisable descriptions of practice are required.

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**APPENDIX**

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**REFERENCES**

Large fistula between right coronary artery and right atrium in a 50 year old asymptomatic woman

A 50 year old asymptomatic woman without prior medical history was found to have a continuous murmur, which was loudest in the lower right parasternal region. Her physical examination and standard ECG were normal. Transthoracic echocardiography revealed mild right ventricular dilatation, with trivial tricuspid regurgitation and transvalvar flow velocity estimated at 2.5 m/s. Left ventricular size and systolic function, and all valves, were normal. A hypoechoic image was identified near the right ascending aortic wall, spherical at its origin, then extending linearly along the right, inferior margin of the right ventricle, without clear termination. Cardiac catheterisation (specially frontal and left lateral views of selective arteriography, performed with a 5 French Amplatz catheter) confirmed the presence of a huge, aneurysmal (measured to 9 mm at its origin), sinuous right coronary artery emptying widely into the right atrium just below the coronary sinus ostium, opacified retrogradely over a few millimetres (black arrow). A small retroventricular arterial branch originated from the anomalous coronary artery (white arrow). Left ventriculography and left coronary angiograms were normal. Right heart and pulmonary artery pressures were normal, though pulmonary output was increased to 7.4 litres/min, with a calculated 1.48:1.0 left-to-right shunt. Exercise stress sestamibi scintigraphy showed normal myocardial perfusion.

This asymptomatic patient was recommended to undergo long term medical surveillance.

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