The Registry of the International Society for Heart and Lung Transplantation: Fourteenth Pediatric Lung and Heart-Lung Transplantation Report—2011

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This Fourteenth Pediatric Lung and Heart-Lung Transplantation Report covers the pediatric lung transplantation and heart-lung transplantation experience from January 1986 through June 2010. During this period, 1,664 pediatric lung transplant procedures and 653 pediatric heart-lung transplant procedures were reported to the International Society for Heart and Lung Transplantation (ISHLT) Registry. It is important to note that recent figures include pediatric lung and heart-lung transplant procedures dating back to 1987 that were previously not reported to the ISHLT Registry but were retrospectively entered in 2010. In 2009, the last complete year included in this year’s ISHLT Registry report, 127 pediatric lung transplant procedures were reported, which is an increase of 43% compared with 2004. These figures, however, include only the pediatric lung transplant procedures that were reported to the ISHLT Registry and do not necessarily reflect the trend in numbers of pediatric lung procedures performed worldwide.

This pediatric lung and heart-lung transplantation report includes a summary of the data analyses performed by the Registry this year and is supplemented by further analyses and additional figures that are available on the ISHLT Registry Web site (www.ishlt.org/registries). This report does not include detailed analyses and figures for pediatric heart-lung transplantation because this information has been presented in previous reports1–3 and the number of pediatric heart-lung transplant procedures continues to decrease (7 procedures in 2009, compared with 10 in 2008). Information on rare indications and rare causes of death after pediatric lung transplantation, as well as on risk factors for death or graft failure after pediatric lung transplantation is also reported elsewhere.1–3 This year’s Registry report presents a more detailed analysis of pediatric lung retransplantation because the number of pediatric retransplant procedures reported to the Registry has increased in recent years.

Statistical methods

Descriptive characteristics were used as appropriate, presenting proportions and medians ± standard deviations or 5th–95th percentiles. Survival rates were calculated by the Kaplan-Meier method and compared with the log-rank test. No adjustments were made for multiple comparisons; whenever the remaining recipient number was < 10, survival graphs were truncated. More detailed explanations of the statistical methodology accompany slides, where appropriate; slides are available online (www.ishlt.org/registries).

Lung transplantation

Volume, indications, and donor characteristics

The number of transplant centers reporting pediatric lung transplant procedures in 2009 increased to 49, compared with 40 in 2008. During the last 5 years, the number of centers reporting pediatric lung transplant procedures in-
increased by 36%, which is likely a partial result of the retrospective data described above (Figure 1). As in previous years, most of the centers (84%) performed fewer than 5 transplant procedures annually; however, for the first time, 3 centers reported 10 to 19 pediatric lung transplant procedures in 2009, accounting for 28% of transplants reported (Figure 2). In 2009, the 3 highest-volume centers performed 28% of procedures reported; then again, 50% of the lung transplant procedures occurred in centers that report fewer than 5 procedures annually (Figure 3).

During the last decade, the number of pediatric lung transplant procedures reported to the Registry increased

![Figure 1](image1.png)  Number of centers reporting pediatric lung transplants to the Registry. Analysis includes living-donor transplants.

![Figure 2](image2.png)  Number of centers reporting pediatric lung transplants by center volume. Analysis includes living-donor transplants.
considerably, from 73 in 1999 to 127 in 2009 (the last complete calendar year included in this year’s report). Most pediatric lung transplant procedures occurred in recipients aged between 12 and 17 years (93 of 127 in 2009; Figure 4), which increased from 60% of all lung transplants in the era 1986 through 1995 to 70% in the recent era 1996 through June 2010 (Figure 5). In 2009, only 3 lung transplant procedures were reported in recipients aged younger than 1 year, which is identical to the figures reported in 2008 (Figure 4).

Figure 3  Number of pediatric lung transplants by center volume. Analysis includes living-donor transplants.

Figure 4  Age distribution of pediatric lung recipients by year of transplant. Analysis includes living-donor transplants.
There are geographic differences in the age distribution of pediatric lung transplant recipients: in Europe, 82% of the procedures between January 2000 and June 2010 were performed in recipients aged ≥ 12 years compared with 65% in North America. In contrast, 4% of the reported lung transplant procedures in this period in Europe were performed in recipients aged ≤ 5 years compared with 15% in North America (Figure 6).

In the period from January 1986 to June 2010, 64% of the pediatric lung transplant recipients received pediatric donor organs (aged <18 years). Only 6% received organs from donors aged ≥50 years (Figure 7). Geographic differences in donor age distribution are noticeable: in Europe, 45% of transplanted organs come from pediatric donors compared with 64% in North America. The proportions in regions outside Europe and North America were similar to those in Europe (Figure 8). In the last 5 years, only 1 pediatric lung transplant procedure from a living donor was reported to the Registry (Figure 9).

Similar to previous reports, the most common underlying diagnosis for children and adolescents (aged <18 years) who undergo lung transplantation is cystic fibrosis (CF). However, differences in age groups can be observed. In children aged ≥ 6 years, CF was the most common diagnosis from January 1990 to June 2010 (Table 1). In children aged 5 years and younger, the most common indications were idiopathic pulmonary arterial hypertension, idiopathic pulmonary fibrosis, congenital heart disease, and surfactant protein B deficiency (Table 1). The overall distribution of indications has not changed notably compared with previous reports. However, regional differences exist in the diagnosis distribution: 55% of transplant procedures in North America were undertaken in pediatric recipients with CF compared with 75% in Europe (Figure 10). Interestingly, the diagnosis of CF accounted for 70% in Europe in last year’s report. The increase in the number of transplant procedures for CF in Europe could partly be explained by the above-mentioned retrospective data entry.

**Immunosuppressive therapy**

The use of induction therapy increased further compared with previous reports. Between January 2001 and June 2010, induction therapy, consisting of anti-lymphocyte globulin, anti-thymocyte globulin, and interleukin-2 receptor antagonist therapy, was used in 60% of the procedures (Figure 11); a decade ago, this was less than 50%. No significant 5-year post-transplant survival difference was noted between recipients who did and did not receive induction therapy (Figure 12).

The use of maintenance immunosuppression is displayed in Figure 13. Tacrolimus use increased further compared with cyclosporine. At the 1-year follow-up, 78% of pediatric recipients received tacrolimus compared with 22% who...
received cyclosporine. As previously reported, mycophenolate mofetil (MMF) is replacing azathioprine as the cell-cycle inhibitor of choice.3 This trend is even more evident in this year’s report: at the 1-year follow-up, 65% of recipients were treated with MMF compared with 30% who received azathioprine. Almost all pediatric recipients continued to receive prednisone as part of their maintenance immunosuppression, even 5 years after lung transplantation. The most common maintenance immunosuppression drug combination was tacrolimus, MMF, and prednisone, which

**Figure 9** Donor type distribution by year of transplant for pediatric lung recipients. Analysis includes living-donor transplants.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Age</th>
<th>No. (%)</th>
<th>No. (%)</th>
<th>No. (%)</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic fibrosis</td>
<td>&lt;1 year</td>
<td>1 (1.2)</td>
<td>5 (4.5)</td>
<td>167 (56.0)</td>
<td>775 (71.7)</td>
</tr>
<tr>
<td>Idiopathic pulmonary arterial hypertension</td>
<td>1–5 years</td>
<td>12 (14.0)</td>
<td>25 (22.5)</td>
<td>30 (10.1)</td>
<td>75 (6.9)</td>
</tr>
<tr>
<td>Retransplant: obliterative bronchiolitis</td>
<td>6–11 years</td>
<td>0</td>
<td>7 (6.3)</td>
<td>9 (3.0)</td>
<td>34 (3.1)</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>12–17 years</td>
<td>13 (15.1)</td>
<td>8 (7.2)</td>
<td>4 (1.3)</td>
<td>9 (0.8)</td>
</tr>
<tr>
<td>Idiopathic pulmonary fibrosis</td>
<td></td>
<td>9 (10.5)</td>
<td>20 (18.0)</td>
<td>13 (4.4)</td>
<td>38 (3.5)</td>
</tr>
<tr>
<td>Obliterative bronchiolitis (not retransplant)</td>
<td></td>
<td>0</td>
<td>10 (9.0)</td>
<td>19 (6.4)</td>
<td>45 (4.2)</td>
</tr>
<tr>
<td>Retransplant (not obliterative bronchiolitis)</td>
<td></td>
<td>3 (3.5)</td>
<td>4 (3.6)</td>
<td>8 (2.7)</td>
<td>27 (2.5)</td>
</tr>
<tr>
<td>Interstitial pneumonitis</td>
<td></td>
<td>1 (1.2)</td>
<td>2 (1.8)</td>
<td>2 (0.7)</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary vascular disease</td>
<td></td>
<td>8 (9.3)</td>
<td>7 (6.3)</td>
<td>3 (1.0)</td>
<td>0</td>
</tr>
<tr>
<td>Eisenmenger syndrome</td>
<td></td>
<td>1 (1.2)</td>
<td>5 (4.5)</td>
<td>5 (1.7)</td>
<td>7 (0.6)</td>
</tr>
<tr>
<td>Pulmonary fibrosis, other</td>
<td></td>
<td>5 (9.8)</td>
<td>5 (4.5)</td>
<td>12 (4.0)</td>
<td>22 (2.0)</td>
</tr>
<tr>
<td>Surfactant protein B deficiency</td>
<td></td>
<td>15 (17.4)</td>
<td>3 (2.7)</td>
<td>1 (0.4)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>COPD/emphysema</td>
<td></td>
<td>4 (4.7)</td>
<td>2 (1.8)</td>
<td>3 (1.0)</td>
<td>9 (0.8)</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td></td>
<td>2 (2.3)</td>
<td>2 (1.8)</td>
<td>6 (2.0)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td></td>
<td>1 (1.2)</td>
<td>0 (0)</td>
<td>5 (1.7)</td>
<td>13 (1.2)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>11 (12.8)</td>
<td>6 (5.4)</td>
<td>12 (4.0)</td>
<td>26 (2.4)</td>
</tr>
</tbody>
</table>

COPD, chronic obstructive pulmonary disease.

*Analysis includes living-donor transplants.
was used in 55% of recipients at the 1-year follow-up and in 47% at the 5-year follow-up, (Figure 14).

**Outcomes**

Survival after pediatric lung transplantation continues to be comparable with that reported in adult lung transplant recipients. We define the transplant half-life as the estimated time at which 50% of all recipients have died. In the period from January 1990 to June 2009, the half-life of adult recipients was 5.4 years compared with 5.5 years in pediatric recipients (Figure 15), although there seems to be better longer-term survival in pediatric patients. The 5-year survival of pediatric lung transplant recipients between January 1990 and June 2009 was 51%. For pediatric recipients who received allografts in the new era between 2002 and June 2009, 5-year survival was 53% and 7-year survival was 45% (Figure 16). In contrast to the previous year’s report, the difference is not statistically significant when survival is analyzed by era; this may be because survival for older cohorts is revised upward compared with previous reports after the retrospective data entry, as described above.

Kaplan-Meier survival analysis by recipient age group shows a significantly better survival of recipients aged 1 to 11 years compared with recipients aged 12 to 17 years (Figure 17). Recipients younger than 1 year have the worst early post-transplant survival within the 3 age groups (<1 year vs 1–11 years vs 12–17 years). Nevertheless, in younger patients surviving at least 1 year after transplant, long-term outcome is comparable with that of other pediatric age groups (Figure 18). Survival analyzed by procedure type is significantly worse for single-lung transplant procedures compared with bilateral lung transplant procedures; however, the number of pediatric single-lung transplant procedures is relatively small (Figure 19).

**Causes of death**

In the first year after lung transplantation, infection (non-cytomegalovirus [CMV]) and graft failure remained the 2 leading causes of death (Figure 20). Beyond the first year after transplantation, bronchiolitis obliterans syndrome (BOS), graft failure, and non-CMV infection were the leading causes of death. Further details regarding causes of death and relative incidences of leading causes of death are displayed in Figure 20 and Table 2. Details about causes of death labeled as “other” were published in the 2008 ISHLT Registry Report and are not presented again this year because the data have not changed considerably.1

**Complications and morbidities**

Hypertension, renal impairment, diabetes mellitus, and BOS remain the most common comorbidities after pediatric lung
transplantation, and all of these increase in prevalence with time after transplantation. Detailed figures of cumulative prevalence of morbidities within 1 and 5 years after transplantation are reported in Tables 3 and 4, respectively, and are similar to the figures presented in last year’s report.3

Severe renal impairment, defined as creatinine > 2.5 mg/dl (221 μmol/liter), dialysis, or renal transplant, develops in 11% of pediatric lung transplant recipients by 5 years after transplantation and in 17% by 7 years (Figure 21); once again, figures were identical with last year’s report.3

By 5 years after transplantation, malignancies have developed in 14% of pediatric recipients, virtually all of which are lymphoproliferative diseases. By 9 years, the cumulative incidence of malignancies increases to 23%, comprising mostly lymphoproliferative disorders but also 2% skin cancer (Figure 22).
BOS, the second most common morbidity within 5 years after transplantation, was reported in 56% of pediatric lung transplant recipients. For the first time, we analyzed freedom from BOS for pediatric lung recipients, stratified by age group and diagnosis. BOS was reported less frequently in younger surviving lung recipients; that is, in 31% of the recipients aged < 1 year compared with 44% in recipients aged 1 to 11 years and 54% of recipients aged ≥ 12 years by 4 years after transplantation (Figure 23). When stratified by diagnosis (CF vs idiopathic pulmonary artery hypertension), cumulative incidence of BOS by 5 years after transplantation was similar between the 2 groups (Figure 24).

The functional status of surviving pediatric lung transplant recipients is very good, with 86% of children having no physician-reported activity limitation even 5 years after transplantation (Figure 25). Further details regarding functional status and re-hospitalization needs of surviving recipients are displayed online (www.ishlt.org/registries).

### Lung retransplantation

In the interval from January 1994 to June 2010, 105 retransplant procedures were reported to the ISHLT Registry. Retransplantation was performed for obliterative bronchiolitis (OB) in 50 patients and for indications other than OB in 51. Most of the retransplantations occurred in recipients aged ≥ 12 years. In recipients with OB, 36 of 50 procedures (72%) were performed in recipients aged ≥ 12 years. Retransplantations for indications other than OB were performed in recipients aged ≥ 12 years in 38 of 51 cases (75%; Table 1).

Regional differences in lung retransplantation activity exist. In Europe, retransplantation was the indication for transplantation in only 3% of the procedures, compared with 7% in North America (Figure 10). Survival after lung retransplantation was worse compared with primary lung transplantation if all indications for retransplantation were taken together and results were not stratified by inter-transplant interval (the time between the primary and the retransplantation).
plant procedure). For pediatric retransplant procedures performed between January 1994 and June 2009, survival was 63% at 1 year, 50% at 3 years and 38% at 5 years (Figure 26). However, when pediatric lung retransplant procedures between January 1988 and June 2009 were stratified by inter-transplant interval (30 at <1 year vs 59 at ≥1 year), the 1-year survival was 39% and 62%, respectively (Figure 27). It is important to note that the analyses included living-donor transplants and only patients who were aged <18 years old at the time of retransplant are included.

Interestingly, when pediatric re-transplant procedures were stratified by diagnosis—51 OB vs 57 non-OB—survival after retransplantation was similar between both sub-groups (Figure 28). Owing to the small number of cases, a survival analysis after pediatric lung retransplantation by era was not feasible. However, this will most
likely change in the future with the increasing number of retransplant procedures performed in pediatric recipients worldwide.

In summary, this ISHLT Registry pediatric lung transplantation report shows that the number of centers reporting pediatric transplants to the Registry and the annual number of pediatric lung transplant procedures are constantly increasing, with a total of 127 lung transplant procedures in 2009. Overall, survival after pediatric lung transplantation is improving, with a half-life of more than 5 years for procedures performed in the last 20 years, comparable to results achieved in adult recipients.

Disclosure statement
All relevant disclosures for the Registry Director, Executive Committee Members, and authors are on file with the ISHLT and can be made available for review by contacting the Executive Director of the ISHLT. All of the figures and tables from this report, and a more comprehensive set of Registry slides are available at www.ishlt.org/registries/.

References