Mortality in pediatric renal transplantation: A study of the French pediatric kidney database


Abstract: Objective and Methods: To assess patient survival in pediatric renal transplantation, we retrospectively reviewed 573 transplants in 553 patients, registered from 1995 to 2005.

Results: Mean age at transplantation was 9.9 years. Patient survival at 1, 5 and 10 years was respectively 99%, 97% and 96%. Death occurred at a median time of 2.6 years after transplantation. Long-term patient survival was significantly lower in recipients younger than 5 years old. Seventeen patients (3.1%) died. Two deaths occurred while under maintenance dialysis. Among the remaining patients, the two main causes of death were infections (33%) and malignancies (27%). Interestingly, initial disease-related complications were a major cause of death (34%).

Conclusion: A low mortality rate was observed, with the majority of deaths due to malignancies and infections, and with a notable participation of complications related to the initial disease. No impact of cardiovascular disease was noted with the given follow-up period. Improvements in managing immunosuppression may contribute to reducing mortality in pediatric renal transplantation.

Renal transplantation is considered as the treatment of choice of ESRD, particularly in childhood. This strategy has been shown to decrease complications related to renal insufficiency, such as growth and delayed cognitive development, and to improve both patient survival and quality of life (1, 2). Moreover, introduction of new immunosuppressive agents and progress in managing immunosuppression over recent decades have led to improvements in graft survival and to a decrease in side effects related to immunosuppressive treatments (3). Despite these advantages, the morbidity and mortality related to transplantation need to be considered. Outcome studies covering large cohorts followed over 10 and 20 yr are now beginning to emerge, reporting on mortality rates and causes of death following renal transplantation in children (4–13). Cardiovascular alterations, malignancies, and infections are the most common causes of death following renal replacement therapy in children. Age and weight of recipient or donor type have also been specifically identified as morbidity and mortality risks after renal transplantation (1), but the impact of the initial disease has rarely been considered in mortality studies.

To assess the mortality rate and causes of death after renal transplantation in childhood, we retrospectively reviewed the renal transplantsations performed in pediatric patients between 1995 and 2005 recorded in a French pediatric database.

Abbreviations: ARPKD, autosomal recessive polycystic kidney disease; DIVAT, Data Computerized and Validated in Transplantation; ESRD, end-stage renal disease.
Patients and methods

Data collection

Clinical and biological data from renal transplantations performed from January 1, 1995 to December 31, 2005 in children under the age of 16 were retrospectively registered in a French pediatric kidney database, DIVAT. Data were available from seven pediatric renal transplantation centers [pediatric departments of the hospitals of Lille, Lyon (some patients were previously included in a cohort mortality study by the Lyon center (9)), Nancy, Nantes, Paris-Necker, Paris-Debré, and Tours]. Combined transplants such as liver-renal transplantations were excluded from the study.

The data collected included recipient characteristics (age and weight at transplantation, extra-renal epuration parameters before transplantation) and transplantation parameters (donor type, cold ischemia duration, HLA mismatching, delayed graft function, immunosuppressive induction, and maintenance therapy). For the deceased children, details concerning initial disease and the circumstances of death were collected by each center directly from the patient’s medical records.

Data analysis

Actuarial graft and patient survival were calculated using Kaplan–Meier analysis. When indicated, actuarial survival curves were compared with a non-parametric log rank test. Values of p < 0.05 were considered statistically significant. Surveys were established without including 40 children lost to follow-up (7.2%). Statistical correlations were performed between death and certain transplantation characteristics including recipient age under five yr, dialysis parameters, HLA mismatching, donor type, delayed graft function (defined as the necessity of one or more dialysis immediately after the transplantation), and cold ischemia duration.

Results

Population

From January 1, 1995 to December 31, 2005, 573 renal transplantations were performed in 553 patients under the age of 16 in these seven centers (with a national global activity of 880 grafts for this era). Main etiologies of ESRD were dysplasia/hypoplasia/obstructive uropathy (40%), glomerulopathy (20%), and hereditary nephropathy (17%) and are reported in Table 1. Mean age and weight at transplantation were 9.9 ± 4.4 yr and 27.6 ± 13 kg, respectively. It was a first transplantation in 92.7% of cases. Second and third transplantations represented 7% and 0.3% of cases. For 15.5% of the children, the renal transplantation was performed in a pre-emptive manner and the mean waiting time for transplantation with a deceased donor was 3.6 months. The majority of transplantations were from deceased donors (86%), whereas living-related donors represented 14%. This distribution was 72% and 28%, respectively, when transplantations were pre-emptive. The primary characteristics are summarized in Table 2.

Immunosuppressive and antihypertensive treatment

Patients received induction therapy with either monoclonal or polyclonal antibody in 92% of cases (data were unavailable for 8%). The maintenance therapy usually consisted of a triple immunosuppression with a calcineurin inhibitor, an anti-metabolite agent and corticosteroids. Changes in immunosuppression regimen were actually observed in this cohort. Cyclosporine A was used in 98% of the cases in the 1995–1997 era and progressively decreased to 60% in the 2004–2005 era. In the same time tacrolimus was more frequently administered. Moreover, mycophenolate mofetil was predominantly used from 2000 onwards. For induction therapy, anti-IL2 receptor was mainly used from 2000 onwards. The follow-up revealed that an antihypertensive treatment was administered in 42.6%, 39.5%, and 36% of the children at one, five, and 10 yr, respectively (data for treatment at one, five, and 10 yr were available for 520/553, 311/386, and 75/122 children).
Actuarial graft and patient survival

The mean time of follow-up for this cohort was 70 ± 37 months; overall actuarial graft survival was 94%, 86%, and 78% at one, five, and 10-yr post-transplantation, respectively, and overall risk of rejection was 36.8% (n = 211). Actuarial patient survival was 99%, 97%, and 96% at one, five, and 10-yr post-transplantation, respectively. Seventeen children died during the study period, corresponding to a mortality rate of 3.1%. Patient survival was significantly worse for recipients under five yr of age as compared with older recipients. The comparison of patient survival considering donor type or dialysis parameters is summarized in Table 3. No significant correlations were established when comparisons of patient survival were performed taking into consideration recipient weight <15 kg, a duration of dialysis up to six or 12 months, the number of transplantations (first or more), a cold ischemia time under 12 or 24 h, an initial delayed graft function or an HLA mismatching (results not presented).

Time and causes of death

The mean age at death was 9 ± 4.2 yr. The median time between transplantation and death was 2.6 yr (range two days to 9.8 yr).

Two children died at 20 and 39 months after graft failure, while they were under dialysis. The cause of death was a cholangitis in the context of an ARPKD and a gas embolism occurring in hemodialysis.

Fifteen children died with a functioning graft. Causes of deaths for these 15 children could be separated into three groups: (i) malignancy, (ii) infections, and (iii) others causes.

Malignancy (27%)
The death was related to malignancy in four cases: three EBV-related lymphomas and one pleural sarcoma. The EBV lymphomas concerned three children transplanted at 0.7, 6.6, and 15.5 yr of age and occurred at 30, 2, and 12 months, respectively, after transplantation. The first child survived more than four yr after the lymphoma diagnosis and died at 7.8 yr, but the two others died precociously after diagnosis at 6.8 and 16.9 yr.

Infections (33%)
This group included five children. In a 10-yr-old child receiving a transplant for an ARPKD, a septic shock occurred 31 months after transplantation. No germ was identified and the potential link to the ARPKD was uncertain. The other four infections were in part related to the initial disease. Two patients with a Schimke syndrome, a rare autosomal recessive disease with a severe innate immunodeficiency, died from infections: one child aged four and a half yr presented a respiratory infection leading to deterioration 11 months after transplantation. The diagnosis of Schimke was known before the renal transplantation and after an induction with polyclonal antibodies; this child thus received an immuno-suppressive treatment without anti-proliferative medication. The other patient died at 9.8 yr, 24 months after transplantation, from a sepsis caused by Stenotrophomonas maltophilia following a disseminated CMV infection and a pulmonary aspergillosis. For this child, the diagnosis of Schimke was made after renal transplantation, in the context of severe infections, osseous dysplasia, repetitive transitory ischemic strokes, and severe pancytopenia. Opportunistic infections recurred despite azathioprine being stopped and the immunosuppressive load being reduced. The fourth child suffered from a mitochondrial encephalopathy and died at 13.5 yr from a severe pulmonary infection, 34 months after transplantation. Finally, one child with spina bifida and a neurological bladder, died at 15.8 yr from a severe sepsis secondary to a urinary tract infection from Pseudomonas aeruginosa, three months after transplantation.

Others etiologies (40%)
Six children died from other causes. One child with a methylmalonic acidemia died at 11.4 yr, 22 months after transplantation, from a pallidus necrosis, occurring a few days after the start of chemotherapy for a hepatoblastoma. Two children died suddenly from unknown causes, one committed suicide, one drowned, and one died following an early postoperative complication (a severe hyponatremia). No cardiovascular-related deaths were observed.

Table 3. Actuarial patient survival (%) at one, five, and 10 yr for the DIVAT registry

<table>
<thead>
<tr>
<th>Years</th>
<th>1</th>
<th>5</th>
<th>10</th>
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<tbody>
<tr>
<td>Global survival</td>
<td>99</td>
<td>97</td>
<td>96</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5 yr</td>
<td>99</td>
<td>94</td>
<td>92*</td>
</tr>
<tr>
<td>≥5 yr</td>
<td>99</td>
<td>98</td>
<td>97*</td>
</tr>
<tr>
<td>Extra-renal epuration parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HD or DP</td>
<td>100</td>
<td>97</td>
<td>95</td>
</tr>
<tr>
<td>Pre-emptive transplantation</td>
<td>99</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>Donor type</td>
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<td></td>
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<tr>
<td>Living donor</td>
<td>100</td>
<td>100</td>
<td>93</td>
</tr>
<tr>
<td>Deceased donor</td>
<td>99</td>
<td>97</td>
<td>96</td>
</tr>
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</table>

*Significant difference (p < 0.05)
Discussion

Renal transplantation had been shown to improve quality of life, cognitive development, and growth velocity in children (1, 2). Thanks to new immunosuppressive treatments and improved management of immunosuppression, patient, and graft survival have notably improved over recent decades. The follow-up of pediatric cohorts and the establishment of data registries are necessary for a better understanding of the causes of graft failure or death and lead us to revisit our practices in transplantation. Clinical data from renal transplantations performed from 1995 to 2005 in seven French pediatric renal transplantation centers were collected in a pediatric kidney transplantation database and analyzed to determine the potential mortality risk factors and the impact of initial disease in pediatric renal transplantation.

Overall actuarial graft survival was 86% at five yr and 78% at 10 yr, which is comparable to other registries (2, 7, 10). Actuarial patient survival in our cohort was 99% at one yr and 96% at 10 yr, reflecting a low mortality rate of 3.1% following a renal transplantation in children. Other recent pediatric renal transplantation cohorts showed slightly different short- and long-term results, probably in part because our study only concerned recent transplantations performed over the last 11 yr, and did not take into account previous transplantations. Table 4 summarizes results observed in previous published cohorts. Nevertheless, mortality is highly influenced by transplantation era so these cohorts cannot be compared if transplantation periods are different.

In our study, the main causes of mortality with a functioning graft were malignancies and infections. This has already been reported in other pediatric transplantation cohorts (2, 7, 10) and could be directly related to the immunosuppressive treatment. The global incidence of lymphoma was 1.8% (10 of 553 patients). Three deaths were caused by an EBV-related lymphoma, which occurred in a median time of 15 months after transplantation in three children of different ages. Compared with the general population, the overall incidence of cancer is 10-fold higher; skin cancer is the most frequent, but mortality is mainly because of non-Hodgkin lymphoma (14). Despite progress made during the last decade in the chemotherapeutic treatment of lymphoma, we highlight here the importance of monitoring recipient EBV status and viral load, and of adapting immunosuppressive treatment to minimize the risk of subsequent post-transplantation lymphoproliferative disorders (15). Infections, mostly bacterial in nature, were also a notable cause of mortality (33%), occurring at a mean of 20 months post-transplantation. Bacterial infections usually occur not only in the first month post-transplant (16) but also beyond the first six months, as already observed in other cohorts (5, 9). Viral and opportunistic infections did not represent a cause of mortality in our cohort except for the children with Schimke syndrome, possibly because prophylactic treatments are now administered during the first months of transplantation (cotrimoxazole for the prevention of Pneumocystis carinii, and antiviral agents for the prevention of EBV and CMV).

Interestingly, when considering all deaths occurring with a functioning graft, complications directly or indirectly related to the initial disease represented one-third (34%) of the causes of mortality. Two patients with Schimke syndrome died from opportunistic infections, which could be considered as complications related to their innate immunodeficiency. Despite the published review of Schimke patients who received a transplant without severe infectious complications (17), according to our results, these children should be considered at a very high risk of mortality after renal transplantation, and the benefits of this treatment should be discussed. Two other patients died from complications of a metabolic disease. In one case, pulmonary deterioration occurred in a patient with a mitochondrial cytopathy and subsequent encephalopathy, and the other child was a young boy with a pallidus necrosis leading to death in the context of methylmalonic acidemia. This rare complication.

<table>
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<th>Transplantation era</th>
<th>Patient survival</th>
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<tr>
<td></td>
<td>1 yr, %</td>
</tr>
<tr>
<td>NAPRTCS 2006 (2)</td>
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<tr>
<td>1987–2005</td>
<td>97.7</td>
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<tr>
<td>&lt;2 yr old</td>
<td>91</td>
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<tr>
<td>Jungraithmayr (3) with mycophenolate mofetil 1996–1999</td>
<td>100</td>
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<tr>
<td>Sózen (5) for living donors 1975–2004</td>
<td>98</td>
</tr>
<tr>
<td>Englund (7) 1981–1991</td>
<td>91</td>
</tr>
<tr>
<td>Grothoff (8) 1972–1992</td>
<td>91</td>
</tr>
<tr>
<td>Harzallah (9) 1987–2002</td>
<td>98.4</td>
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<tr>
<td>Mehrabi (10) 1967–2003</td>
<td>95</td>
</tr>
<tr>
<td>Van Damme (13) 1980–2000</td>
<td>94</td>
</tr>
<tr>
<td>Neipp (21), &lt;15 kg 1974–1999</td>
<td>93</td>
</tr>
<tr>
<td>DIVAT 1995–2005</td>
<td>99</td>
</tr>
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seemed to be related to previous and long-term insufficient control of the metabolic disorder (18). Of note, this pallidus necrosis occurred at the beginning of chemotherapy for a hepatoblastoma, a malignant hepatic cancer not known to be related to immunosuppression. The fifth death could also be considered as a consequence of the initial disease because it was a severe sepsis caused by a urinary tract infection in a child with spina bifida. Neurologic bladders and subsequent obstruction of urinary excretion are important risk factors for severe urinary infections with septicemia, septic shock, and death.

Of note, this study did not reveal an impact of cardiovascular disease in mortality, in contrast to other pediatric cohorts (2, 4, 6, 12). This might be one of the reasons for the low mortality rate observed here. The cardiovascular risk factors in patients with ESRD are arterial hypertension, left ventricular hypertrophy and arterial and valvular calcifications. Although the incidence of left ventricular hypertrophy and hypertension decreases after transplantation, risk for cardiovascular disease persists (19). In our cohort, only 39.5% and 36% of the patients were treated for hypertension at five and 10 yr following transplantation, which is lower than in other registries (2, 7, 8). The median time on dialysis before transplantation was 16 months, which is relatively short. These reasons may explain, in part, the low cardiovascular mortality rate in our study, all the more because the follow-up was over a maximum of 10 yr, a relatively short period for cardiovascular consequences. In the LERIC cohort, mean age at death was higher (18 yr), reflecting the longer follow-up than our study, sometimes up to 20 yr (8).

The only potential mortality risk factor in our cohort was a young age at transplantation, with worse patient survival observed for recipients younger than five yr of age at the time of transplantation. This was also shown in the NAPRCTS report (2) and in cohorts of young recipients, with a weight below 15 or 20 kg at the time of transplantation (4, 12). The role of donor type on patient survival is not well determined, except for young recipients (20), but in our study had no influence on patient survival. At least, mean delay between dialysis and transplantation did not significantly affect mortality in this cohort, as has already been reported (6).

This retrospective study showed a low mortality rate after renal transplantation in a multicenter pediatric cohort. Although malignant disease and infections were major causes of death, complications related to the initial disease were also a notable cause of mortality. In contrast, no impact of cardiovascular disease was noted with the given follow-up period. These results should encourage an improvement in the management of immunosuppression in children after renal transplantation, to reduce the causes of mortality. We now have to follow this cohort over a longer period to note the long-term mortality rate and to better evaluate the long-term effects of immunosuppression, notably on the incidence of cancer, and the possible repercussions in terms of cardiovascular disease. Moreover, efforts to collect data in our French database should be prolonged to enable further studies in pediatric renal transplantation.

Acknowledgments

We hereby acknowledge all present and previous members of the French Pediatric Nephrology Society that have collected data in DIVAT, as well as Pascal Daguin and the Roche Laboratories, who have contributed to the management of DIVAT. We also thank Dr. J. Ashton-Chess for editing the manuscript.

References