Pediatric renal transplantation.
A lifelong renal transplantation

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INTRODUCTION

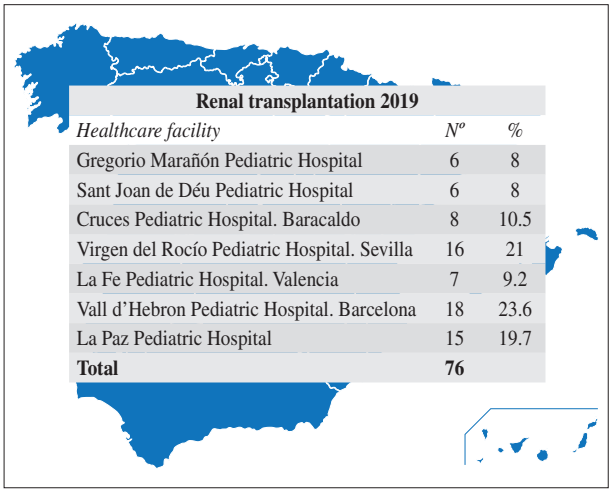
Renal transplantation (RT) represents a revolution in the lives of end-stage renal disease (ESRD) children. When conservative ESRD treatment is no longer feasible, RT stands as the best option, since it has some advantages over dialysis.

Even though it does not heal ESRD definitively, a functioning renal graft allows all kidney dependent functions to be recovered, improving children's growth, neurological development, and quality of life, as well as that of their families[1,2].

Since RT was first carried out in a child[3] in the 50s, results have progressively improved, and the number of patients benefiting from this treatment has surged. Indication criteria for RT in the pediatric population have been expanded over time. And since RT-associated mortality is lower than that of dialysis[4], RT is increasingly being carried out at a younger age. Conversely, contraindication criteria for RT in children are virtually zero and limited to the presence of tumor, acute infection, or chronic infection acute stage.

According to the European Registry of Dialysis and Transplantation, 4.6 patients per million population (pmp) under 15 years old are engaged in a renal replacement treatment program (dialysis or transplantation) every year. The proportion of children under 5 years old has increased in the last years, from 4.7% to 14% of all children undergoing RT[5]. The Spanish Pediatric Registry of Renal Replacement Treatment (REPIR I) includes 5.5 patients pmp under 18 years old annually, which represents 60-65 patients a year.

In addition, donated organs are a scarce resource. The reduction in the number of potential donors noted in the last years makes supply insufficient given the current demand. The lack of organs has become the main stimulus to look for new donation sources.



Renal transplantation 2019

Healthcare facility	*Nº*	*%*
Gregorio Marañón Pediatric Hospital	6	8
Sant Joan de Déu Pediatric Hospital	6	8
Cruces Pediatric Hospital. Baracaldo	8	10.5
Virgen del Rocío Pediatric Hospital. Sevilla	16	21
La Fe Pediatric Hospital. Valencia	7	9.2
Vall d'Hebron Pediatric Hospital. Barcelona	18	23.6
La Paz Pediatric Hospital	15	19.7
Total	**76**	

Figure 1. Distribution and number of pediatric RTs carried out in Spain in 2019 (ONT).

Most RTs, both in adult and in children, are carried out with cadaveric organs[6]. Donation rate in EU member states remains stable, around 13.1 per million population (pmp). Spain had been the leading European country in terms of donations for years, with 32.5 donors pmp, and it has been the world leading nation since 2018, with 48 donors pmp.

According to the Spanish National Transplantation Organization (ONT), 3,423 RTs were performed in 2019, 76 of which were carried out in pediatric patients, which accounts for 2.2%. In Spain, there are 7 healthcare facilities where pediatric RTs are conducted. Some RTs are performed as part of an adult program, while some others are carried out within pediatric programs only. However, all healthcare facilities benefit from a specialized cross-disciplinary team (Fig. 1).

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Globally speaking, access to RT varies widely and depends on how economically developed each nation is[7,8]. In Spain, contrarily to what used to happen some years ago, the inclusion of living donors (LDs), the expansion of donation criteria, and the acceptation of pediatric priority in the distribution of cadaveric organs have allowed for a quicker access to RT.

RT survival in pediatric patients is considered the best in all transplantations. RT results have significantly improved in the last two decades[9,10]. 1-year post-renal graft survival in pediatric recipients is approximately 94% with cadaveric donors (CDs) and approximately 96% with LDs, whereas 5-year post-renal graft survival is approximately 73% with CDs and approximately 81% with LDs (Fig. 2).

Given the few renal transplantations carried out in each pediatric healthcare facility, multicenter studies (NAPRTS, UNOS, OPTN, UKT, ANZDATA)* prove particularly interesting, since they allow a significant number of patients to be assembled. In the United States, some 800 RTs are conducted in patients under 18 years old annually.

The objective of this work is to gather pediatric RT highlights following the end of transplantation *Era IV* (2010-2017), where all efforts are aimed at finding the ideal organ for each recipient and minimizing immunosuppressive therapy side-effects in order to improve long-term graft survival.

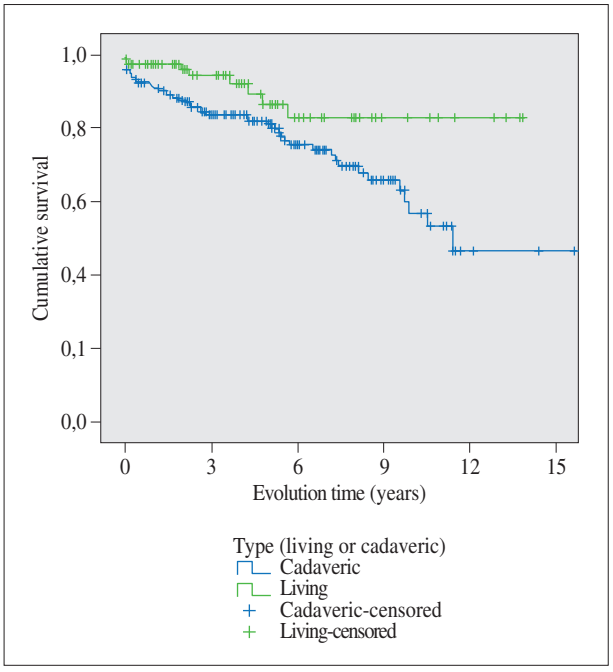


Figure 2. LD *vs.* CD renal graft actuarial survival. La Paz Pediatric Hospital, Madrid (Spain), 2017.

DONOR

Donor source

Renal transplantation with LDs

It is performed across the world, but in different proportions. Transplant nephrectomy is a safe procedure with a very low intraoperative risk for the donor (0.03-0.06%)[11]. This risk seems reasonable given the socioeconomic advantages for the recipient and the improvement in their quality of life, especially in children. Having an organ ready for transplantation may help avoid dialysis. 25-30% of RTs conducted in pediatric patients are anticipated (pre-dialysis)[12,13].

A significant increase in the number of transplantations carried out with a LD relative (father or mother) in younger pediatric recipients has been noted in the last years[14,15]. In our view, this is due to the advantages of using kidneys from living donors (shorter dialysis time, improved donor-recipient histocompatibility, and shorter cold ischemia time, among others), which allow for longer graft survival. The good results of laparoscopic nephrectomy for kidney removal purposes has also been a key reason for this increase[16] (Fig. 3).

However, even though LD RT results are better than CD RT results, only 20% of pediatric RTs within the EU are LD RTs[5,17].

When a potential living donor is available for a first RT, one cannot help but wonder about the most adequate organ use policy, since the potential donor will most likely require re-transplantation.

Data from the NAPRTS[9] and the ANZDATA[10] suggest that second transplantation results are better when the first transplantation has been carried out with a cadaveric donor and the second has been performed with a living donor, as compared to second transplantation results when the first transplantation has been carried out with a living donor and the second transplantation has been performed with a cadaveric donor, or when both transplantations (first and second) have been conducted with a cadaveric donor. In addition, re-transplantation is more frequent when the first transplantation has been carried out with a CD (30%) than when it has been performed with a LD (11%).

One should also bear in mind that the use of a LD in the first transplantation – whether a relative of the recipient

**The North American Pediatric Renal Transplant Cooperative Study (NAPRTS); The United Network for Organ Sharing (UNOS). Organ Procurement and Transplant Network (OPTN); United Kingdom Transplant (UKT); Australia and New Zealand Dialysis and Transplant Registry (ANZDATA).*

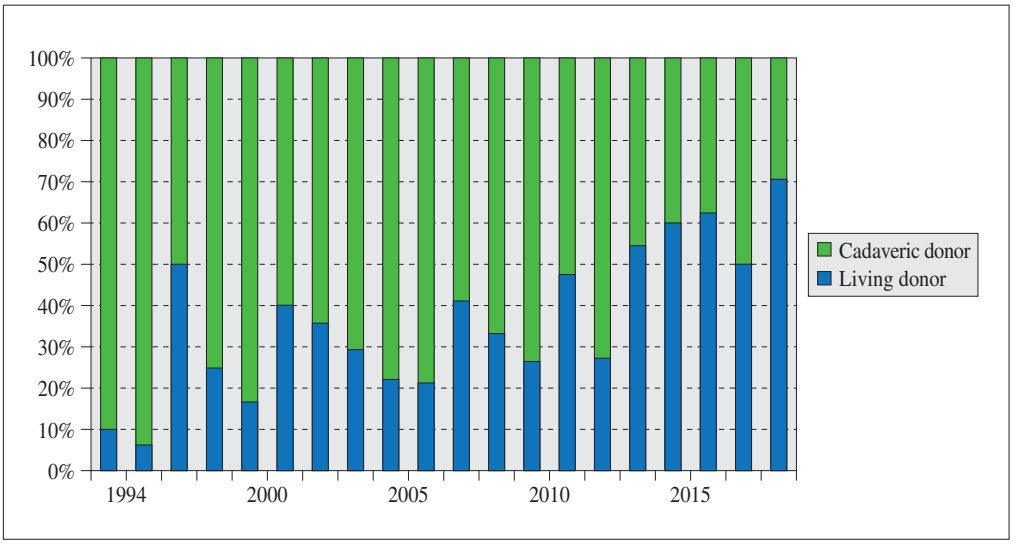


Figure 3. LD impact on global transplantation activity. LD vs. CD annual percentage. La Paz Pediatric Hospital, Madrid (Spain), 2018.

or not – provides with a longer graft survival than the use of a CD. Moreover, it cannot be guaranteed that LDs will always be available for the children in the future.

We advocate the use of LDs as a first option in children whenever LDs are available.

Non-heart-being donor renal transplantation

Owing to the lack of organs, transplantation programs have had to expand donation criteria and use marginal organs. The impact of non-heart-beating donor organs on graft survival is currently being assessed.

In these circumstances, and contrarily to brain-dead donors, donation is carried out following cardiac arrest. Death occurs in a controlled manner to optimize organ viability and reduce hot ischemia time (Maastricht III) as much as possible[18]. These organs have a higher risk of delayed graft function, since hot ischemia time is longer than in brain death donation[12,19].

In adults, renal transplantation with non-heart-beating donors and renal transplantation with brain-dead donors have demonstrated similar results in terms of survival. However, results in pediatric recipients are still unclear. Few RTs with this type of donors have been carried out, with few and inconsistent data available in the literature, especially regarding graft survival beyond 4 years[19,20].

Overall, caution should be exercised when using this type of donors in children, since long-term graft survival is more important in pediatric patients.

Donor age

Renal grafts from cadaveric donors under 6 years old are associated with a greater percentage of early graft loss and shorter short-term survival, especially in case of donors under 3 years old[13]. If the number of donor glomeruli is too low to adequately filter the recipient's blood volume, the graft will attempt to adapt through hyperfiltration[21], which is associated with glomerular hypertrophy followed by sclerosis and progressive renal function loss.

According to the NAPRTCS[9], the worst survival results are associated with transplantations carried out with kidneys from cadaveric donors under 2 years old and over 50 years old. The use of kidney donors under 2 years old has been reduced to barely 1%. However, given the lack of organs available for pediatric RT, some programs prefer en-bloc transplantation[22] or simultaneous double transplantation[23] (both kidneys transplanted into the same recipient) in order not to lose the young donor and avoid hyperfiltration by transplanting a larger renal mass (Fig. 4).

Histocompatibility

As it is the case with the adult population, a good donor-recipient HLA compatibility, either with a CD or with a LD, is associated with longer graft survival[15].

Most genes involved in the immune response are located in chromosome 6, in the so-called major histocompatibility complex, which includes human leukocyte antigen genes (HLA system). Before the patient is put on the waiting list, the recipient's HLA antigens are identified in all RT candidates to quantify the number of HLA antigens shared by the potential donor and the recipient. The most important HLA antigens in the transplantation process are HLA DR, B, and A.

Poor compatibility can make long-term graft survival shorter and even increase the risk of immune sensitization following graft loss[24], producing anti-HLA antibodies that could have a negative impact on future transplantation survival. According to the OPTN, the best results are achieved when the donor and the recipient have no incompatible antigens or when compatibility is identical in the 6 HLA loci[25].

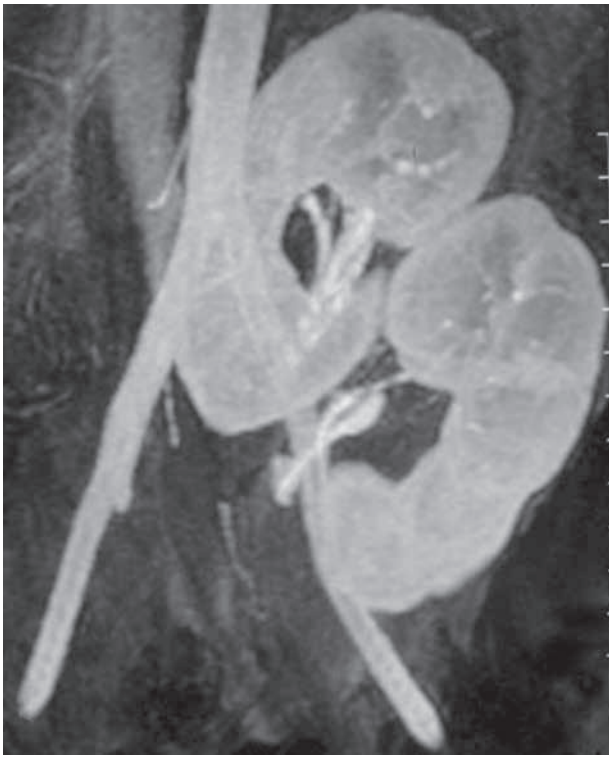
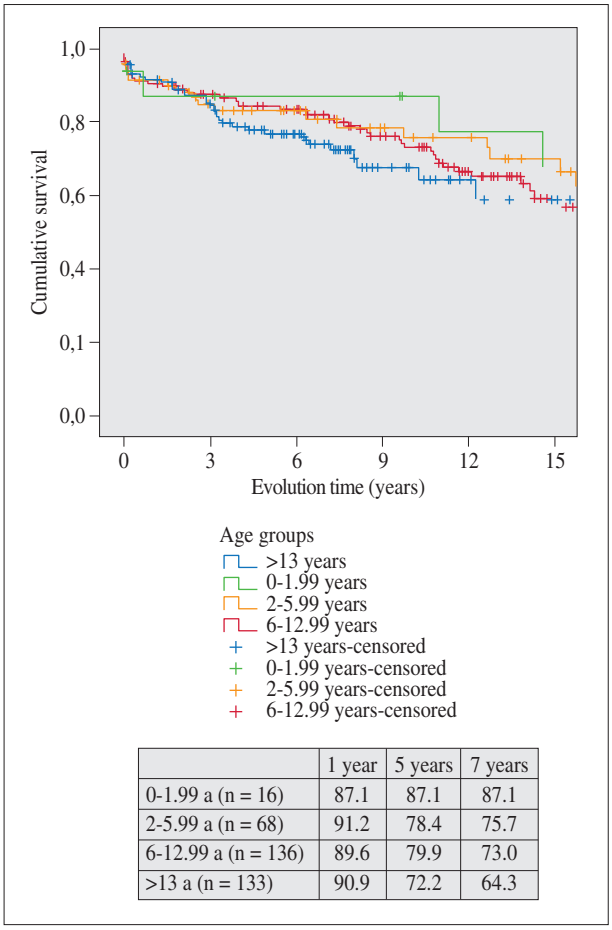


Figure 4. Double renal implant in FII. 2-year-old cadaveric donor.



	1 year	5 years	7 years
0-1.99 a (n = 16)	87.1	87.1	87.1
2-5.99 a (n = 68)	91.2	78.4	75.7
6-12.99 a (n = 136)	89.6	79.9	73.0
>13 a (n = 133)	90.9	72.2	64.3

Figure 5. Renal graft actuarial survival according to recipient age. La Paz Pediatric Hospital, Madrid (Spain), 2017.

RECIPIENT

Recipient age

Age has a significant impact on transplantation results. There are two specific age groups potentially impacting graft survival for very different reasons. One group is that of recipients under 2 years old. These patients are more likely to have vascular thrombosis and a higher incidence of acute rejection episodes[26]. However, thanks to the advances made in pediatric anesthesia and intraoperative care, and to the inclusion of microsurgery in vascular anastomoses, thrombosis incidence has significantly decreased in these recipients over the last years. In addition, the new immunosuppressants have also helped in reducing the number of rejection episodes[27,28].

The other risk group, which is less well-known, is that of adolescent recipients, where graft loss percentages are higher, typically as a result of lack of therapeutic compliance and the fact that this age coincides with a transition period to adult units[29,30]. The percentage of late acute rejection episodes in patients aged 13-17 years old is higher than in any other age group (Fig. 5).

Primary renal disease

The most frequent causes of ESRD in children are dysplasia and hypoplasia, followed by obstructive uropathy and glomerulonephritis.

Much of the damage suffered by the native kidney, particularly bladder dysfunction associated with posterior urethral valves, will also be suffered by the transplanted kidney if not repaired prior to RT[31].

Children with history of long-term central catheter, mainly in the femoral veins, as well as patients undergoing abdominal mass surgery (Wilms tumor) are more likely to have iliocaval venous thrombosis**.** Identifying these issues before transplantation is key to design the correct surgical strategy[32] (Fig. 6).

Focal glomeruolosclerosis, atypical hemolytic uremic syndrome, and membranoproliferative glomerulonephritis are more likely to reoccur in the graft and cause transplantation failure[15].

IMMUNOSUPPRESION

The introduction of new drugs such as tacrolimus and mycophenolate with a greater immunosuppressive effect has improved renal graft survival, reducing rejections.

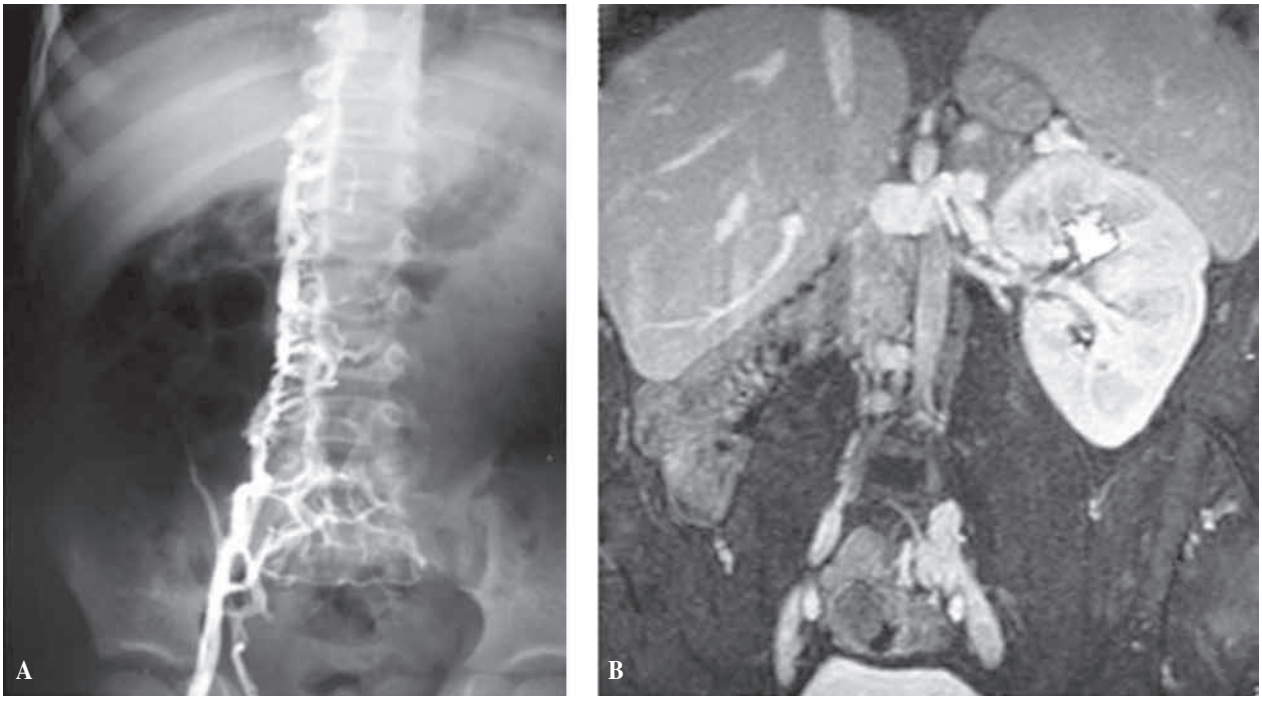


Figure 6. Iliocaval venous thrombosis. A) Ascending venography in a RT candidate. B) Orthotopic renal transplantation.

However, it has also increased the risk of infection and lymphoproliferative disease (1-7%).

Antibody induction therapy, introduced in pediatric RT's immunosuppressive protocol in the 90s, has been demonstrated to prevent or at least delay acute rejection episodes in the first months post-transplantation. This therapy is carried out with monoclonal antibodies, and in high immune risk recipients, it is performed with polyclonal antibodies.

The most frequently used maintenance treatment or therapy includes steroids, tacrolimus, and mycophenolate mofetil[1,13]. These treatments are similar both for LD RT and CD RT.

Immunosuppression, which is key for graft tolerance, is not free of adverse effects. In the last decades, steroid dosage has been progressively reduced and even suppressed in some protocols to avoid morbidity and impact on growth. Contrarily to what was observed in the cyclosporine era[33], the use of tacrolimus has allowed steroid dosage to be reduced without a significant increase in acute rejection episodes[13]. However, steroid repercussion on post-transplantation size, cardiovascular risk, and esthetic appearance has not been determined[1,34]. Treatment fails in 13% of patients receiving a low steroid dosage or steroid-free protocol, so patients have to resume the usual therapy[1].

The development of a treatment allowing for immune tolerance in the recipient while significantly reducing or even avoiding immunosuppressants with no rejection risk is undoubtedly the most expected advance in the field. Various groups[35,36] have recently demonstrated that the deferred use of specific hematopoietic derivatives in RT is able to generate tolerance – a state where donor and recipient immune systems coexist (mixed chimerism). Tolerance induction in transplanted patients can change the long-term survival of the transplanted organ and help achieve the goal of lifelong renal transplantation.

REJECTION

Rejection is the most frequent cause of renal transplantation failure in children[9,10]. Rejection risk decreases with a good donor-recipient histocompatibility and immunosuppressive treatment.

Acute rejection episodes significantly increase the risk of developing chronic rejection and graft loss[15,37]. At least 46.9% of pediatric RTs will have a rejection episode throughout the graft's life (42% in LDs and 53% in CDs). Chronic rejection is the most important cause of long-term graft loss[13] (35%).

Immunosuppressants have demonstrated to be able to prevent and treat acute cellular rejection, significantly reducing acute rejection episodes. However, results are not so good in antibody-mediated rejection and humoral rejection[13].

Rejection episodes in adolescents are mostly due to therapeutic non-compliance. They are highly aggressive, mixed rejections, both humoral and cellular[29,30].

Chronic rejection and nephrotoxicity, especially as a result of calcineurin inhibitors, are associated with

chronic graft nephropathy. The latter is defined as a slow and progressive deterioration of renal function, accompanied by variable proteinuria, and not attributable to other causes.

CONCLUSIONS

Donors are a scarce resource that should be optimized. Numerous factors have an impact on graft survival, but immune and surgical advances in the last decades have led to a significant improvement in graft and patient survival. However, long-term results are insufficient, so it is our great challenge to improve them.

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