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Review

Pediatric Renal Transplantation

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Abstract

Indications, procedures, complications, pharmacokinetics and outcomes of renal transplantation are different in children and adults. Subjects <18 year-old, are often included in a list apart, benefiting from donors <15 year-old and the waiting-time is reduced to <12 months in 71% of the cases. The risk of thrombosis limits the use of donors <2 years and the transplantation in small children <1 year-old. One third of children is transplanted at age less than 5 year-old. Living-related transplantation (LRT) is common in USA (57%) and in Northern Europe often pre-emptive before entering dialysis (24%). The immunosuppressive treatment tends to reduce doses and duration of steroids, optimizing induction therapy with IL-2R inhibitors and using tacrolimus or mycophenolate or sirolimus. Patient survival is better in transplanted children than in adults (94-98% at 5 years). Infections, cardiovascular diseases and neoplasia induced 34%, 15% and 12% of deaths respectively at 10 years; morbidity for infections and lymphoprolipherative disease is increasing in parallel with the effectiveness of anti-rejection therapy. Acute rejections decreased from 70% in 1987 to 31% in 2002 in cadaveric transplantation (CT) and renal survival at 3 years increased from 50% in 1985 to 82% for CT and up to 92% in LRT. In adolescents (11-17 year-old) renal survival is lower than in small children and in adults 18-65 year-old. Renal losses are due to chronic transplant nephropathy (32%), vascular thrombosis (13%) and recurrence of original nephropathy (focal glomerulosclerosis recurs up to 50%, membrano-proliferative glomerulonephritis in 30%, primary hyperoxaluria in 90% if combined kidney-liver transplantation is not performed). Growth improves after transplantation particularly in children < 5 years, while it is not completely satisfactory in adolescents. Overall results indicate that kidney transplantation in children has improved very much and will offer in the next future even more favourable outcomes.

Keywords: paediatric transplantation, paediatric nephropathies, renal transplantation therapy, renal transplantation complications, renal transplantation survival

Introduction

It is well known that indications, endpoints, procedures, complications, pharmacokinetic and outcomes of renal transplantation are different for children than they are for adults. In responses to these differences, dedicated paediatric Registries collecting data of paediatric kidney transplants have been developed, including the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS), who assembled since 1987 to 2002 about 6773 data of transplanted children in USA [1-3], and cooperative groups as the Cooperative Clinical Trials in Pediatric Transplantation (CCTPT). The comparison of outcomes in adults and children is very important to improve results in both cohorts. Like in other Countries, in Italy the National Transplantation Centre (NTC) has developed a particular paediatric section in the national data-base common to all the ages, accomplishing at a national level the data collection initiated in 1987 by the Paediatric Group of the North Italian Transplant Program (NITp) on 493 pediatric renal transplants [4-6].

Pediatric donor

According to the Italian low, the diagnosis of cerebral decease has to be confirmed by the total absence of the cerebral circulation in children < 1 year old, where the observation time must be > 24 hours; in potential donors aged >1 year and < 15 years the observation time must last more than 12 hours.

The donor age is critical for children's transplantation. There are no major limitations of using kidneys of bigger size than that of the recipient, while the risk of renal vein thrombosis limits the use of donors <2 years and the transplantation in small children < 1 year-old. For this reason, in several Centres including most of the Italians, a ration between potential donor/recipient weight is calculated and a target ratio of >0.8 is taken into account at recipient choice. In the Italian Registry on 231 children transplanted in the period 1998-2002 a weight ratio < 0.8 was reported in 17% only of the cases, >0.8 < 1.2 in 25% and >1.2 in 58% of children transplants.

The renal vein thrombosis represents the major non-immunological cause of renal graft lost in the pediatric age [7,8]. This is partially related to the recipient age (33% in children <1 year-old, 11% in those >1 year and <2 year-old), but mostly it depends on the young age and small size of the donor and particularly on the disproportion of renal vessels being smaller in the donor. For these reasons donors aged less than 10 years were reported to be reduced from 35% to 10% since 1987 to 2000 in USA. The utilization of donors less than 2 year-old fell down from 3.5% to 0.9% [9] and in UK donors < 3 year-old have no longer been used since 1994 and only 22% were >3 < 5 year-old in a Sick Children Hospital report in 1999. In USA donors aged less than 6 years have been only exceptionally used, while in Italy the limit is generally for children < 2 year-old but

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smaller children are not excluded at priory, since en-block kidney transplantation may be performed. The frequency by age of cadaveric donors (data in Italy during the observation period 1998 – 2002) is 20% of donors less than 5 year-old, 59% of children aged between 6 and 14 years and 21% of donors >14 year-old. According to statistical calculations in UK data, the donor age <5 years carries a Relative Risk of 4.6 to lose the renal function in 3 years.

Paediatric Waiting List

In Italy there is a national waiting list for all children < 18 year-old needing renal transplantation. The recipient is selected by an informatics' program that calculates the score in base on the clinical and immunological data (ABO blood group and HLA matches). The average waiting time is a few months for younger children (within 5 year of age), a few years for adolescents. Recent data report that in Italy the average waiting time is 0-12 months in 71%, 13-36 months in 24% and more than 36 months only in 11% of children needing renal transplantation.
In USA donors <18 year-old represented in 2002 some 15% of all the kidney donors and exceeded the need for the uremic paediatric population. The waiting list is common for both adults and children and the donations are shared among all the suitable recipients; however children go to the top of the list after 6-18 months of unsuccessful waiting. With this system in USA the average waiting time during 2002 for children aged 6-10 years was 379 days and for 11-17 year-old the adolescents 415 days, a significantly shorter waiting time in comparison with adults (1000 days in average).

Need for renal transplantation in children

The incidence of end-stage renal failure in children has increased in USA in the last 10 years by 20%, similarly to data in 18-34 year-old young adults (27%) [10,11]. This increase is mild in comparison with the three fold increase for people 50-64 year-old and the five fold increase for subjects > 65 year-old. As result, children represent in USA only the 1.4% of patients in waiting list, while ten years ago they were the 2.5%. Among children waiting transplantation the age distribution is stable, mostly (70%) represented by 11-17 year-old adolescents. The Italian national paediatric list, updated to January 2005, included 55 children, none under 18 months of age and under 8 kg of weight: 18% were < 5 year-old, 14% were between 5 and 9 years, 38% between 10-15 years, and 30% were > 16 years-old. Children smaller than one year- old unusually enter a waiting list either in USA or in Italy.
The incidence of deaths in the waiting list is particularly high for children aged less than 5 years, who have a death incidence similar to that seen for more than 50 years old persons waiting for kidney transplantation. Whereas adults and elderly patients in waiting list have a higher co-morbidity, the mortality of children is relevant.

Nephropathies leading to uraemia and need of renal transplantation in children

The primary diagnosis of renal diseases leading to end stage renal failure (Table 1) differs among various age groups: in children < 2 year-old the most common causes of uraemia are malformative nephro-uropathies (aplasia, severe renal hypo-dysplasia, obstructive uropathy, usually associated with abnormal organogenesis) or congenital nephropathies (familiar nephrotic syndrome, as Denis-Drash syndrome, or metabolic diseases like primary hyperoxaluria) [11,12]. In the older age group (2-8 years) the most common are hereditary diseases with longer course (like renal polycystosis or nephronophthisis) and acquired diseases, like focal and segmental glomerular sclerosis. In older children and particularly in adolescents the acquired nephropathies prevail over congenital forms. In the American black people lupus erythematosus and focal and segmental glomerular sclerosis are the more frequent cause of chronic renal failure [13,14].

Table 1. Primary diagnosis of end stage renal disease in paediatric recipients

	%
Obstructive uropathy	16
Ipo-dysplastic kidneys	16
Reflux nephropathy	6
Prune - Belly Syndrome	3
Nephronophthisis	3
Polycystic Kidneys	3
Focal segmental glomerulosclerosis	12
Chronic Glomerulonephritis	4
Congenital Nephrotic syndrome	3
Hemolytic Uremic Syndrome	3
Others	36

A condition peculiar to paediatric renal transplantation is the presence of associated bladder disorders/hypoplasia (as in case of posterior urethral valve obstructive uropathy), reported in about 20-30% of the cases. In these children the most important problem is, either before the transplantation or after, to reconstruct the "reservoir" of the bladder, making it continent and able to be voided in the less invasive way. The improvement of bladder and urethra reconstruction in children with neo- bladder or urethral derivation, has allowed achieving the same survival after renal transplantation as in children without these malformations. It has been recently suggested that bladder and urethral reconstruction could be done after a successful renal transplantation, which will allow a urine flow able to efficiently rehabilitate the bladder.

Choice of living or cadaveric donor

"Pre-emptive" transplantation, done before dialysis (in 24% of children in USA, one third of which receiving a living related donation) is far more frequent in USA or in Northern Europe than in Italy or in Southern Europe. The waiting list for cadaveric donor is not accessible in Italy as well as in most European Countries before entering the chronic dialysis treatment and living donor transplantations are uncommon before dialysis. Living related transplantations (LRT), used to be very common in USA since long time, are further increased in these last years: from 1987 to 2002 the percentage of LRT is increased from 42% to 57%. Donors are in above 40% of the cases one of the parents, but also grandparents are common donors and in the last years the donation from unrelated donors has increased [13]. This percentage is higher than adult LRT in

USA, which is already elevated (41% LRT in adults in 2002). The percentage of LRT is inversely proportional to the receiver's age: 100% of LRT in babies < 1 year, 60% in those > 1 year and <10 years, 50% in patients > 11 year-old. In Italy LRT accounted in 1998-2002 for 7.5% of renal transplantation in children, and the donor was always a receiver's parents, except one case in which the donor was a brother [6].
An important aspect to consider is that renal graft function could not last for decades and the child could need another kidney transplants. A study satellite to the ERA-EDTA Registry investigated, in children that received two subsequent renal transplants, whether the outcome was better when receiving first LRT or cadaver transplantation (CT). There was no significant statistic difference and the general behaviour of Paediatric Nephrologists in Italy and in Southern Europe is to wait until a cadaver donor is available for the first transplantation: in case of failure, the LRT from parents is encouraged. Several variables influence this choice, which should be discussed according to individual needs. However, as increase in LRT even as pre-emptive transplantation is likely to further increase also in Southern Europe in a next future.

Children age at renal transplantation programming

Kidney transplantation is exceptional in children under the age of 2 years, also in USA in spite of the pioneering activity of the Minneapolis Centre [15] and it represents 5% of all the paediatric transplantations. Most children (80%) receive a renal transplantation when they are >6 year-old. In Italy since 1987 to 1999 the median age of transplanted children was 13,7 years and only 7% was under 5 years. More recently, in 1998-2002, an increased transplantation in the younger subjects was reported, as 21% of kidney grafts were performed in children aged between 0-5 years, 33% between 6-12 years and 48% between 16-18 years.
Renal transplantation in less than 2 year- old children has limited indications, since risk for both kidney and recipient survival was reported to be too high. Centres that more than ten years ago begun the program of small baby transplantation - subjects < 1 year-old weighting some 6 kg - highlighted an increased risk for death (1 year-survival of about 90% for LRT and 79% for CT) and for kidney loss due to renal vein thrombosis. Complications were particularly frequent when donors were small children, eventually weighting more than the donor [15]. Results have been recently improved [16,17] using low molecular weight heparin, or selecting living adult donors only and using a particular surgical technique placing the graft not in the common extra-peritoneal location, but intra-peritoneally performing the vascular anastomosis with vessels larger than the iliac ones (like aorta, cava). At any rate, the choice of grafting so young children is exceptional and even in USA only 18 transplants in children less than 1 year-old were registered from 1996 to 2000.
There is no definite age-limit for renal transplantation, but taking into account the life risk and the good results obtained with peritoneal dialysis and adequate nutritional support [19] most Centres choose to wait until the child grows up to put him in the waiting list for transplantation. The risk decreases progressively and after the first year of age it is severe but not so high to discourage the transplantation and by 18 months of age the transplant success becomes likely. The risk for children older than 3 years is within the average and does not differ from adolescents.
The USA Registry NAPRTCS recently reported greatly improved results in children younger than 2 years, but we have to consider that the number of the very young babies transplanted is extremely limited and related to excellence Centres, highly specialized in this field [15].
In Italy the good outcomes obtained with peritoneal dialysis and the high risk of kidney transplantation in very young children suggest a waiting attitude till the age of 18-24 months.

Surgical technique

In general, renal transplantation is technically similar in children and in adults, as anastomoses with the iliac vessels are performed in extra peritoneal approach. In very small children the kidney is sometimes located in intra peritoneal seat, after mobilising the right colon to enlarge the suitable area, performing a latero-lateral anastomosis with the inferior vena cava and the distal aorta; but this is very rare, like exceptional is the "en-bloc" bilateral renal transplantation at the same time.
Extremely rare is the nephrectomy of the native kidneys, unless they would be bigger for severe polycystic kidney disease where the room for a new kidney is reduced.
During the period 1998-2002 in a total of 231 paediatric transplants, cold ischemia time was very low, less than 20 hours in almost the totality of the patients.

Immunosuppressive treatments in paediatric renal transplantation

The basal protocol of immunosuppressive treatment for paediatric renal transplantation changed in the last years. The NARPTCS reported that the use of polyclonal and monoclonal antibodies against T cells has almost completely disappeared: given in 28% and 14% respectively in 1997, they are now employed in 4% and 1% respectively.
The use of the monoclonal antibodies anti IL-2 receptor (IL-2R) has increased in USA as well as in Italy. The NAPRTCS report indicates that, among the children transplanted in 2003, 38% received basiliximab, 22% daclizumab, 7% anti-thymocytes/anti-lymphocytes and 31.7% did not receive any induction therapy, but this last group is going to disappear [3,20].
In the years 1998-1993 almost 90% of the children registered in USA, were on maintenance therapy with corticosteroids (C), azathioprine (AZA) and cyclosporine (CSA). Over the time we assisted to a revolution of this therapy for the progressive entry of new drugs and now only 15% of the children is taking the traditional treatment (C, CSA, AZA). The 2003 NAPRTCS report indicated that among children transplanted in 2002 some 42% received CSA, 52% tacrolimus (TAC), 67% mycophenolate mofetil (MMF), 19% sirolimus (SIR) and 1% AZA [3,21]. In parallel to the improving of short-term graft survival due to the effectiveness of the new drugs, particularly when given in association, major attention is going to be focused on long-term graft survival and general wellbeing of the transplanted children trying to avoid the therapy side effects.
Special aim of paediatric transplantation is to reduce as minimal as possible steroids. The C has been for long time

considered unique for rejection prevention, particularly in children. Since C selective target is cellular immunity, this drug has been considered a "sine qua non" for transplant therapy. However the severe side effects (increased infection vulnerability, Cushing's face, hypertension, dyslipidemia and diabetes, vascular complications, digestion and emotional disorder…) are even worse in children than in adults as C depresses the growth velocity. Moreover, this treatment is poorly accepted particularly in adolescents due to worsening of the physical aspect leading to drug self-reduction, and the increased risk of cardiovascular is unacceptable for a population with a long life expectancy like transplanted children [27]. Therefore steroids are going to be reduced in most paediatric protocols, which generally use an induction therapy with 10 mg/kg methylprednisolone followed by prednisone at rapidly reduced dosages of 0.12-0.15 mg/Kg/day within 6 months from the transplantation.

The first approach was to try to stop C after 6 months in children with stable renal function, who were on CSA and AZA. The results were at the beginning not favourable for an increase in acute rejections (AR) [20]. More recently retrospective analyses on children with strongly indications to stop the steroid therapy due to the severe clinical contraindications showed that the C stop was related to a good outcome, particularly when TAC was given. In fact some prospective trials with induction therapy by IL-2R inhibitory followed by TAC and MMF, where the steroid was stopped by 6 months, showed very good results with a significant reduction of the side effects of the corticosteroid therapy and minimal increasing of the AR.

On the basis of these encouraging results a prospective trial with C interruption at 6 months is now ongoing in USA in children who failed to show AR in the first 6 months: patients are randomized to treatment with CSA or TAC associated to SIR.

Another ongoing USA protocol completely avoids C that are substituted by the first six months after transplantation, with daclizumab therapy plus TAC and MMF [21].

CSA maintains a large use in the paediatric kidney transplant. Several studies were focused on pharmaco-kinetics of CSA in children to identify the best way to monitor this drug. The area under the curve (AUC 0-4) is the most precise method to measure the body exposition to CSA. Considering the number of blood samples needed to calculate AUC which is unsuited to children, investigations were made to use, like in adults, the CSA bloody levels at the second hour (C2). When C2 was > 1700 ng/ml after three months the 80% of transplanted children didn't have AR, versus 60% that presented C2 < 1000 ng/ml. The target C2 to limit chronic rejection is still under evaluation [23].

TAC aroused great interest in paediatric transplantation for the possible use on mono-therapy, explored by the Pittsburgh group, allowing the steroid saving, which was cooled by the increasing of post transplant lymphoproliferative disorders (PTLD) [24], above all in EBV negative children, that received a kidney from a EBV positive donor. After a dosage reduction, the results were more satisfying and presently no increase PTLD frequency has been registered for TAC versus other immunosuppressive drugs. The dosage generally used is 0.10-0.15 mg/Kg/day, modifying the dosage on basis of TAC trough level, with levels around 10-15 ng/ml in the first month and decreasing to 6-10 ng/ml for maintenance. The comparison between TAC and CSA for the prevention of AR in paediatric kidney transplantation was at the beginning in favour of TAC plus C and AZA. When AZA was substituted by MMF the difference between CSA and TAC was no more evident. The follow-up at 2 years revealed some advantage of TAC, but this is still under discussion. TAC could be used combined with SIR, and for the strengthening of the effects, a reduction of the target level is possible. Since the calcineurin inhibitors, either TAC or CSA, have similar nephro-/neuro-toxic effects, in USA ongoing protocols are aimed to avoid calcineurin inhibitors using different combinations of C, MMF and SIR in living donor transplants.

MMF has had a rapid success in paediatric renal transplantation, like for adults, often substituting AZA, even if it is 6-7 times more expensive than the old drug. Even if the reduction by 50% of AR, observed at the beginning in adults, was not confirmed in children, a prospective 3-year study with a combination of MMF/CSA/C showed an important reduction of AR and a graft survival increased to 98% [25]. It is possible that MMF, more efficient, could reduce the need for CSA in children. The currently most largely adopted dosage is 1200 mg/m^2 /day. The curve most predictive for drug exposition considers C0, C1 and C4. The dosage is generally modified according to the clinical immunosuppressive effect. MMF was reduced in 14% of the case for gastric intolerance. The new gastro-resistant formulation needs less adjustment (only in 7%). The MMF blood level measurement proved that the association with TAC produces levels allowing dosage reduction.

SIR is metabolized, as CSA, by Cytochrome P450 and by Glycoprotein P. The simultaneous administration of both drugs amplifies levels and effects (SIR increased to 67-85%) allowing a decrease in SA dosage, with likely limitation of side effects. Assuming SIR 4 hours after CSA this super effect is reduced, and the simultaneously administration is recommended to reduce drug dosage. On the other hand SIR and TAC can be administrated simultaneously because they do not interfere. The relevant immunosuppressive effect of SIR enhanced the search for calcineurin-free protocols [26]. SIR significant decreased AR incidence, and it is of particular interest both in adults and children, because of its potential anti-fibrosis effect in chronic allograft nephropathy (CAN). A protocol is ongoing in USA to investigate the potential benefit of SIR on chronic rejection in children who previously experienced AR, randomized in two groups of traditional triple therapy or SIR [27]. In the last years the Italian Paediatric Centres agreed to use protocols, designed in collaboration, with the purpose to validate the outcomes of the drugs of new generation, including induction therapy by anti IL-2R, CSA and MMF, followed by SIR, stopping MMF, in association with reduced dosages (50%) of calcineurin inhibitors.

Child and transplanted kidney survival

The innovative introduction of new immunosuppressive drugs, as well as improvement of surgical procedures and knowledge of infectious and vascular complication led to significant progress in children renal transplantation outcomes. The survival of children after renal transplantation is generally better than for adults, and 5 years after transplantation it is around 99-98% in LRT and CDT respectively for 6 to10 year-old children (Figure 1, 2).

Adolescents have a lower 5-year survival (96-97% respectively). Also the survival of very young recipients (< 5 year-old) is worse than the other children age groups [9]. In the Italian Registry for renal transplantation in children, the survival of children less than 3 year old was of 97% in 1998-2002 period. No significant differences for patient survival are presently found in LRT and CT.

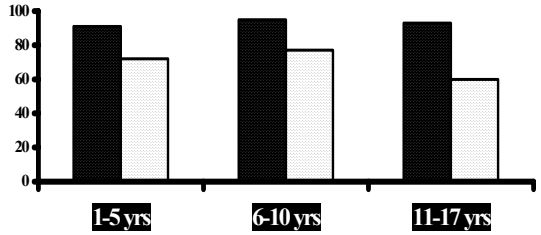

Fig. 1. Graft survival at first (black column) ad fifth year (white column) of living related pediatric kidney transplantation divided by age groups (2003 Annual Report USA Registry OPTN/SRTR)

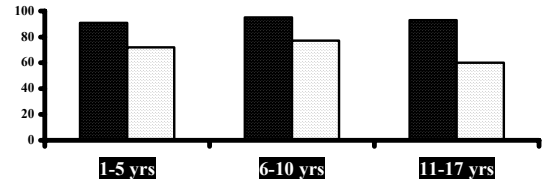

Fig. 2. Graft survival at first (black column) ad fifth year (white column) of cadaveric pediatric kidney transplantation divided by age groups (2003 Annual Report USA Registry OPTN/SRTR)

The most important causes of death in children after 10 years of transplantation include infections (33%), cardiovascular disease and the neoplasm (Table 2). More recent data indicate an increase in mortality due to the bacterial and fungal infections and lymphoprolipherative disease (PTLD) [24,28].

Table 2. Childrens' mortality 10 years after Renal Transplantation

	%
Infections	33
Neoplasms	25
Infarction	10
Hepatitis	10
Stop medications	10
Cerebral hemorrhage	2
Medullary aplasia	2
Others	8

Graft survival

Over the last decade the frequency of AR went to a dramatic reduction: the probability of AR by the first 12 months after renal transplantation, changed from 70% and 57% for CT and LRT respectively in 1987 to 63% and 49% in 1991 and settled down to 31% and 27% respectively in 2002. The relative risk of AR was related to HLA mismatch, the lack of the induction therapy, and the black race [9,29,30]. Moreover, also the severity of the rejections decreased and a complete regression of serum creatinine level, observed in 52% of children years ago, changed to the present 65%.

In 2002 the lost of paediatric grafted kidney due to AR was 4% and 6% in LRT and CT respectively. The treatment for AR in 57% of the cases recorded by the NARPTCS registry consisted in 3 methylprednisone pulses of 20-25 mg/kg every other day. One third of cases were treated with mono-polyclonal antibodies. The reversibility of the AR was related with the age of the child and with the occurrence of the episode in the first year after grafting.

Also the renal survival has improved: survival at one year in the USA registry improved in the last 5 years either in CT or LRT. LRT survival changed from 91% to 94%, from 1987-95 to 1996-2000; and CT improved in parallel from 81% to 93% ($p<0.001$). More recent analyses show CT graft survival has improved so much to cancel the difference of graft survival with LRT. The survival improvement at one year reflected on the survival of the next years: in CT the 3-year survival increased from 50%, in the period 1980-1985 and 65% in 1986-1991, to 82% presently (Figure 2). Results are better in case of LRT: the 3-year survival increased to 92%. The projection of renal function maintenance in children with a stable renal function at one year (t1/2) was 15.4 and 9.5 years for LRT and CT respectively in 1987-1989, increasing in 1996 to 25.4 and 16.4 years, respectively.

The data available from Italian Registry referred in the 1998-2002 period [on 231 children transplants] a renal survival of 92.6% and 89.4% at 1 and 3 years, respectively.

The results in the very young child, less than 1 year- old, improved during these years, from a patient survival of 88% and 78% in LRT and CT respectively in the 1990-1995 years to 96% and 94% in 1996-2000.

The graft survival is better in children < 10 years old child, which has a longer kidney half- life, particularly when adult-size kidneys are used. Furthermore those with a functional kidney at one year, show a long-term prognosis better than older children. These results are certainly related to the improvement of the surgical technique, to the more accurate selection of the donors (rejecting the smallest ones), to the more efficient immunosuppressive and anticoagulant treatments (with a large use of low molecular weigh heparins) and to the development of specific research programs, for paediatric patients.

The general improving of the paediatric transplants is established by the minimal necessity of dialysis during the post transplant period (12% in USA) in comparison with adults (24%).

Table 3. Causes of pediatric transplanted kidney lost (North Am Coop Study) 1987-1999 = 6534 pediatric Transplants (*Ped Transplant, 2001; 5:215-231)*

	%
Primary non function	3
Vascular trombosis	13
Technical problems	2
Hyperacute rejection	1
Acute accelerate rejection	3
Acute rejection	16
Chronic rejection	31
Primary disease relapse	6
Death with good renal function	10
Others	15

On the opposite, more recent analysis indicates worst results in the adolescents, where poor drug compliance leads to unexpected results [31]. In 11-17 year- old recipients the 5 year-survival is lower not only in comparison with younger children but also in comparison with adults, except for elderly ones (>65 years old). These adolescents have an excellent short time renal graft survival (at 3 months -1 year), but show a terrible dropping at 3-5 years. The reasons of these awful results are not completely clear and it seems that other factors could be involved beside incompliance. Unexpected vascular thrombosis and the relapse of the renal disease (as Focal Segmental Glomerular Sclerosis) could be involved. At any rate the adolescents group is presently that experiencing the higher renal graft lost.

Causes of renal graft loss in children

Several causes, both immunological and not immunological, can lead to graft loss in children. Rejection of the transplanted organ, with its different expressions, is certainly the most important factor both in European and USA case analysis: it accounts for 50-60% of cases, even though modern drugs have reduced its incidence.
Thanks to new immunosuppressive drugs, the incidence of AR has been significantly lowered, but the incidence of CAN, which represents, like in adult transplantation, the most important cause of graft loss in long term follow-up, accounting for 32% of definitive functional losses, is still high.
Non immunological causes of graft loss includes vascular thrombosis, responsible for 13% of function losses in the USA registry and particularly common when the recipient is less than 3 year-old, even more when the donor is smaller than the recipient. At multivariate analysis several factors increase the risk of thrombosis, including previous treatment with peritoneal dialysis, second transplantation, donor less than 6 years old, more than 24 hours of cold ischemia, recipient less than 2 year-old.
Another important cause of renal graft loss is the recurrence of the primary disease, in particular focal and segmental glomerulosclerosis (FSGS), membranoproliferative glomerulonephritis (MPGN) and primary hyperoxaluria [32,33].
Recurrence of FSGS in the transplanted kidney is certainly the most dramatic problem in Paediatric Nephrology. Several registries underline the fact that FSGS incidence is increasing year by year; being presently FSGS the most common acquired cause of disease in children leading to uraemia, dialysis and transplantation. This nephropathy is particularly common and aggressive in African-American children. Recurrence is reported in 14-50% and increases up to 80-100% of the cases at second transplantations, after a first graft loss due to FSGS recurrence. African-American race, very short history of disease leading to dialysis and positive result for the search of permeabilizing factor are at particular risk. Also the histological aspect of widespread mesangial proliferation associated with FSGS typical lesions is correlated with a higher incidence of recurrence. The role of a living donation by a relative is discussed, also taking into account that common advantages of LRT versus CT are not observed in FSGS case analysis. An average of one third of patients with FSGS looses the transplanted kidney because of rejection, but the outcome is even worse in adolescents: it is not clear whether a pivotal role is played by poor compliance, more frequent in this age group. None of the proposed therapies reaches unanimous consent. The most effective reported treatment is presently plasmapheresis (5-13 sessions, started as soon as recurrence is detected, daily for 3 days, then every other day until proteinuria is lowered to < 0.5 g/day); results are noticed within 5-27 days. A refining of plasmapheresis is plasma adsorption on Protein A-sepharose column [32], which is able to selectively bind and remove a plasmatic fraction endowed with permeability effects on isolated glomeruli. Another approach is cyclosporine given by continuous e.v. infusion 3 mg/kg/day, starting when proteinuria is detected and pursued until remission or for 3 weeks, and then given orally to maintain trough levels at 200-300 ng/ml. Remission was obtained using this protocol in 14/17 children within 28 days after recurrence and remission and good renal function were maintained at long term follow-up. These high doses of cyclosporine are prescribed to overcome the lack of cyclosporine pharmacological effect in dyslipidemic conditions, as in nephritic syndrome due to FSGS recurrence. A combination of high doses of cyclosporine and plasmapheresis seems to be the most efficient protocol. Also the association of Cyclophosphamide, 2 mg/kg for 2 months achieved some positive results. TAC instead has no effect in these conditions.
Membranoproliferative GN recurs in 30% of children, with function loss of the transplanted kidney in one third of cases. Recurrence of the dense deposits form (type 2 MPGN) is especially frequent (88% of cases). Recurrence of atypical haemolytic uremic syndrome (not related to intestinal infection and verotoxin contacts, but induced by mutation of genes encoding for H factor of complement with loss of a natural inactivator, or mutation of genes that codify for the protease that cut Von Willebrand factor – ADAMST), are very common.
The increased frequency of recurrence in transplanted kidneys of children affected by Systemic Lupus Erithematosus or IgA nephropathy, or GN secondary to Schoenlein-Henoch syndrome is more debated. In particular Schoenlein-Henoch syndrome seems to be prone to recurrence, often limited to the kidney, without systemic symptoms. As far as primary hyperoxaluria is concerned, since the metabolic defect is often the missing function of an enzyme produced by the liver, combined transplantation of liver and kidney had been proposed: the outcome was excellent; instead, in isolated kidney transplantation, oxalosis recurs in 90% of cases, with frequent kidney loss.
Finally, organs can be lost due to poor compliance to regular assumption of drugs; in relation to this aspect, the Adult Nephrologist, who often takes care on patients who have already been transplanted in childhood and may not be aware of the severity of the problem during adolescence, plays a key role. Adolescents have the lowest kidney survival on long term follow-up, both in the LTR and CT case analysis; furthermore, they have the lowest percentage of complete functional recover after the treatment of an AR episode. Also recurrence of the original disease is worse in adolescents than in younger children. Several factors contribute to poor compliance, mostly the observation that drugs worsen physical aspects of transplanted kids and despondency deriving from a post-transplantation course characterized by many small to big problems. All the specialists of the field agree on the fact that improving the outcomes in adolescents represents the goal for the upcoming years.

Morbidity of the transplanted child

The morbidity of the transplanted child is similar to that in a transplanted adult (Table 4) in respect to the recurrent bacteria and viral infections which is the more relevant, as more efficient became the immunosuppressive treatment. The new target of the recent therapy is to reduce infections, especially CMV and HBV infections, involved in the pathogenesis of PTLD and with the risk of cancers.

Table 4. Morbidity in transplanted patients

	%
Bacterial infections	13
Viral infections	16
Hypertension	50 at 1 year, 75 at 3 years
Lymphoms	2
Neoplasms	2
Post-transplant-lymphoproliferative disorders (PTLD)	2

PTLD happens in 4.5% of the pediatric renal transplants and the RR is quadruple in comparison with the adult renal transplants [34]. In a pediatric Italian study (NITp) the incidence of cancers in renal transplanted children was 2.2% in total, mostly were PTLD (1.3%) but also urothelial carcinoma, Wilms tumor, dysgerminoma, glioma [16]. The cardiovascular risk is increasingly important [35], due to the increasing of the follow up in renal transplanted children, and echocardiogram is an important screening exam [36].

The growth

One of the most important results of the paediatric transplant is the effect on the height growth. Above all the average height of children at the moment of the transplant is improved, thanks to the specific supportive therapy for end-stage renal failure in children, (by the correction of anaemia, uremic-osteodystrophy and caloric implementation by nocturnal enteric-nutrition, when the spontaneous introduction is insufficient) and, finally by the use of recombinant growth hormone, during the pre-transplant period, if necessary. The children growth improves after transplant, but not in the first year, when the cortico-steroid treatment affects the renewal of growth.

Afterwards the recovery of a normal renal function, the improvement of the uremic-osteodystrophy, the correction of the anaemia, acidosis and vitamin D production exert a positive effect on the growth recovering the retardation related to uraemia [37]. After the first year from the transplant and especially when it is possible to follow protocols with low or absent steroids, the growth restarts quite well. The growth after transplants is as better as younger is the child (< 5 years), instead it is unsatisfactory in teenagers.

Comparing the data of children transplanted before the puberty with those transplanted after, the average growth velocity increased in the first group from 4.9 to 8 cm /years, with a final average height of 0.8 SD in the first two years after transplant. But even if the peak of the growth velocity at the puberty is significant higher than normal children, the total final height at the puberty is lower in 20% of the cases, due a minor length of the pubertal spurt. The final height is 1.3 SD higher in children transplanted before the puberty and only 0.7 SD higher in teenagers transplanted during the puberty. With the actual supportive therapy the final height, among the patients transplanted in paediatric age, growth is normal in 68%, between the mean and – 2SD from the mean. The results as a whole are reasonable but not optimal yet. It is evident that the more the child is close to the stop of the growth, the more it is difficult to obtain significant improvement.

A great interest was played by the possibility to improve the growth by using rhGH, the human recombinant hormone. This therapy was looked with a certain suspect in the paediatric application for the possibility that a growth factor administration could be a risk factor for leucosis in a population already at risk for the immunosuppressive treatment and that could stimulate acute rejection. Clinical studies did not confirm theses adverse assumptions, so the rhGH can be rather safely administrated to transplanted children. The results are in general encouraging but the great individual variability indicates that it is possible that a transplanted child could stop the rhGH treatment at the moment of the transplant and than, after a slow growth in the period immediately after the transplant, could start growing without rhGH [38,39].

The future of the renal transplanted child

A very interesting study, made by the Centres who firstly transplanted a relevant cohort of children (San Francisco and Paris), reported positive results concerning the reintegration in the work and social world of 296 persons who received a kidney transplantation 25 years before [40]. The outcomes were satisfied: 53% worked at full time, only 19% were unemployed. The family life was not so different from the average in healthy subjects: 39% was married or divorced, 18% had children. The 84% thought to be socially independent and 89% felt satisfied. The actual problem for one third of them was the rather short final stature, but it must be taken into account that these subjects were children in a pre-GH, pre- erythropoietin and pre-OH3 Vitamin D period.

The paediatric renal transplantation needs a careful therapy and scruple periodic visits. The past decade has seen substantial improvement in this treatment which is only way to get a complete rehabilitation for the unfortunate child who develops a progressive chronic kidney disease.

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References

1. Benfield MR, McDonald R, Sullivan EK, et al. The 1997 Annual Renal Transplantation in Children Report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). Pediatr Transplant 1999; 3(2): 152-67.
2. McDonald R, Ho PL, Stablein DM, *et al*. Rejection profile of recent pediatric renal transplant recipients compared with historical controls: a report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). *Am J Transplant* 2001; 1(1): 55-60.
3. Benfield MR, McDonald RA, Bartosh S, et al. Changing trends in pediatric transplantation: 2001 Annual Report of the North American Pediatric Renal Transplant Cooperative Study. Pediatr Transplant 2003; 7(4): 321-35.

4. Sirchia G, Poli F, Cardillo M, Scalamogna M, Rebulla P, Taioli E, Remuzzi G, Nocera A. Cadaver kidney allocation in the north Italy transplant program on the eve of the new millennium. *Clin Transpl* 1998: 133-45.
5. Sirchia G, Mascaretti L, Poli F, Scalamogna M, Pappalettera M, Pizzi C. Cadaver kidney transplantation in the north Italy transplant program in the nineties. *Clin Transpl* 1995: 241-54.
6. Cardillo M, Poli F, Barraco F, De Fazio N, Rossini G, Boschiero L, Nocera A, Rigotti P, Marchini F, Zacchello G, Zanon G, Sandrini S, Chiaramonte S, Maresca C, Caldara R, Messa P, Berardinelli L, Ambrosini A, Montanaro D, Rampino T, Minetti E, Gotti E, Ghio L, Ginevri F, Albertario F, Scalamogna M. Renal transplantation. Strategies to prevent organ rejection--the role of an inter-regional reference center. *Contrib Nephrol* 2005; 146: 1-10. Review.
7. Magee JC, Bucuvalas JC, Douglas G, *et al*. Pediatric transplantation. *Am J Transplant* 2004; 4(suppl.9): 54-71.
8. McDonald RA, Smith JM, Stablein D, et al. Pretransplant peritoneal dialysis and graft thrombosis following pediatric kidney transplantation: a NAPRTCS report. Pediatr *Transplant* 2003 Jun; 7(3): 204-8.
9. Drukker A. Renal transplantation and long-term graft survival for all children and adolescents with end-stage renal failure. *Pediatr Transplant* 2004 Aug; 8(4): 313-6.
10. Lewy JE. Treatment of children in the U.S. with end-stage renal disease (ESRD). *Med Arh* 2001; 55(4): 201-2.
11. Seikaly MG, Ho PL, Emmett L, *et al*. Chronic renal insufficiency in children: the 2001 Annual Report of the NAPRTCS. *Pediatr Nephrol* 2003; 18(8): 796- 804.
12. Mitsnefes M, Ho PL, McEnery PT. Hypertension and progression of chronic renal insufficiency in children: a report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). *J Am Soc Nephrol* 2003; 14(10): 2618-22.
13. Neu AM, Ho PL, McDonald RA, *et al*. Chronic dialysis in children and adolescents. The 2001 NAPRTCS Annual Report. *Pediatr Nephrol* 2002; 17(8): 656-63.
14. Bartosh SM, Fine RN, Sullivan EK. Outcome after transplantation of young patients with systemic lupus erythematosus: a report of the North American pediatric renal transplant cooperative study. *Transplantation* 2001; 72(5): 973-8.
15. Khwaja K, Humar A, Najarian JS. Kidney transplants for children under 1 year of age - a single-center experience. *Pediatr Transplant* 2003; 7(3): 163-7.
16. Groothoff JW, Cransberg K, Offringa M, van de Kar NJ, Lilien MR, Davin JC, Heymans HS; Dutch cohort study. Long-term follow-up of renal transplantation in children: a Dutch cohort study. *Transplantation* 2004; 78(3): 453-60.
17. Johnson RJ, Belger MA, Briggs JD, Fuggle SV, Morris PJ; UK Transplant Kidney and Pancreas Advisory Group. Renal transplantation in the UK and Republic of Ireland. *Clin Transpl* 2000: 105-13.
18. Warady BA. Should the DOQI adequacy guidelines be used to standardize peritoneal dialysis in children? *Perit Dial Int* 2001; 21 Suppl 3: S174-8.
19. Warady BA, Ho M. Morbidity and mortality in children with anemia at initiation of dialysis. *Pediatr Nephrol* 2003; 18(10): 1055-62.
20. Tejani A, Ho PL, Emmett L, *et al*. Reduction in acute rejections decreases chronic rejection graft failure in children: a report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). *Am J Transplant* 2002 Feb; 2(2): 142-7.
21. Neu AM, Ho PL, Fine RN, *et al*. Tacrolimus vs. cyclosporine A as primary immunosuppression in pediatric renal transplantation: a NAPRTCS study. *Pediatr Transplant* 2003; 7(3): 217-22.
22. Silverstein DM.Risk factors for cardiovascular disease in pediatric renal transplant recipients. *Pediatr Transplant* 2004; 8(4): 386-93.
23. Pape L, Ehrich JH, Offner G. Advantages of cyclosporin A using 2-h levels in pediatric kidney transplantation. *Pediatr Nephrol* 2004; 19(9): 1035-8.
24. Dharnidharka VR, Douglas VK, Hunger SP, *et al*. Hodgkin's lymphoma after post-transplant lymphoproliferative disease in a renal transplant recipient. *Pediatr Transplant* 2004; 8(1): 87-90.
25. Pape L, Ehrich JH, Offner G, *et al*. Long-term follow-up of pediatric transplant recipients: mycophenolic acid trough levels are not a good indicator for long-term graft function. *Clin Transplant* 2004; 18(5): 576-9.
26. Flechner SM, Kurian SM, Solez K, Cook DJ, Burke JT, Rollin H, Hammond JA, Whisenant T, Lanigan CM, Head SR, Salomon DR. De novo kidney transplantation without use of calcineurin inhibitors preserves renal structure and function at two years. *Am J Transplant* 2004; 4(11): 1776-85.
27. Lai WJ, Chiang YJ, Chen Y, Chu SH. Is sirolimus a safe alternative to reduce or eliminate calcineurin inhibitors in chronic allograft nephropathy in kidney transplantation? *Transplant Proc* 2004; 36(7): 2056-7.
28. Dharnidharka VR, Stablein DM, Harmon WE. Post-transplant infections now exceed acute rejection as cause for hospitalization: a report of the NAPRTCS. *Am J Transplant* 2004; 4(3): 384-9.
29. Gipson DS, Ferris ME. A measure of success in kidney transplantations. *Pediatr Transplant* 2004; 8(2): 104-5.
30. Pape L, Offner G, Ehrich JH, *et al*. Renal allograft function in matched pediatric and adult recipient pairs of the same donor. *Transplantation* 2004; 77(8): 1191-4.
31. Smith JM, Ho PL, McDonald RA. Renal transplant outcomes in adolescents: a report of the North American Pediatric Renal Transplant Cooperative Study. *Pediatr Transplant* 2002; 6(6): 493-9.
32. Baum MA, Ho M, Stablein D, *et al*. Outcome of renal transplantation in adolescents with focal segmental glomerulosclerosis. *Pediatr Transplant* 2002; 6(6): 488-92.
33. Seikaly MG. Recurrence of primary disease in children after renal transplantation: an evidence-based update. *Pediatr Transplant* 2004; 8(2): 113-9.
34. Shroff R, Rees L. the post-trasnplant lymphoproliferative disorder- literature review. *Pediatr Nephrol* 2004; 19: 369-377.
35. Nocera A, Ghio L, Dall'Amico R, Fontana I, Cardillo M, Berardinelli L, Zanon GF, Scalamogna M, Zacchello G, Valente U, Ginevri F. De novo cancers in paediatric renal transplant recipients: a multicentre analysis within the North Italy Transplant programme (NITp), Italy. *Eur J Cancer* 2000; 36(1): 80-6.
36. Matteucci MC, Giordano U, Calzolari A, Turchetta A, Santilli A, Rizzoni G.Left ventricular hypertrophy,

treadmill tests, and 24-hour blood pressure in pediatric transplant patients. *Kidney Int* 1999; 56(4): 1566-70.
37. El-Husseini AA, El-Agroudy AE, El-Sayed MF, *et al*. Treatment of osteopenia and osteoporosis in renal transplant children and adolescents. *Pediatr Transplant* 2004; 8(4): 357-61.
38. Fine RN, Stablein D, Cohen AH, Tejani A, *et al*. Recombinant human growth hormone post-renal transplantation in children: a randomized controlled study of the NAPRTCS. *Kidney Int* 2002; 62(2): 688-96.
39. Acott PD, Pernica JM. Growth hormone therapy before and after pediatric renal transplant. *Pediatr Transplant* 2003; 7(6): 426-40.
40. Bartosh SM, Leverson G, Robillard D, Sollinger HWLong-term outcomes in pediatric renal transplant recipients who survive into adulthood. *Transplantation* 2003; 76(8): 1195-200.