

Paediatric Renal Transplantation

Rosanna Coppo, Alessandro Amore, Licia Peruzzi,
Giovanni Conti, Luca Roasio

Nephrology Dialysis and Transplantation Unit.
Regina Margherita Hospital, Turin, Italy

SUMMARY

Indications, procedures, complications, pharmacokinetics and outcomes of renal transplantation are different in children and adults. Subjects <18 years old often have their own list and benefit from donors <15 years old, meaning the waiting time is reduced to <12 months in 71% of cases. Risk of thrombosis limits the use of donors <2 years old and transplantation in children <1 year old. One third of children aged less than 5 years old are transplanted. Living-related transplantation (LRT) is common in the USA (57%) and in Northern Europe, and is often pre-emptive before starting dialysis (24%). The immunosuppressive treatment tends to reduce doses and duration of steroids, optimizing induction therapy

with IL-2R inhibitors and using tacrolimus, micophenolate or sirolimus. Patient survival is better in transplanted children than in adults (94-98% at 5 years). Infections, cardiovascular diseases and neoplasia were the cause of 34%, 15% and 12% of deaths respectively at 10 years and morbidity due to infections and lymphoproliferative 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 was up to 92% in LRT. In adolescents (11-17 years old) renal survival is lower than in small children and in adults aged 18-65 years old. Renal losses are due to chronic transplant nephropathy (32%), vascular thrombosis (13%) and recurrence of original nephropathy (focal glomerulosclerosis recurs in up to 50% of cases membrano-proliferative glomerulonephritis in 30% and primary hyperoxaluria in 90% if combined kidney-liver

Received for publication: 01/08/2005

Accepted: 29/09/2005

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 greatly improved and will offer even more favourable outcomes in the near future.

Key Words: 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 response to these differences, paediatric Registries solely dedicated to collecting data of paediatric kidney transplants have been set up, including the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS), which gathered data on approximately 6773 transplanted children in the USA¹⁻³ from 1987 to 2002 and cooperative groups such as the Cooperative Clinical Trials in Paediatric Transplantation (CCTPT). The comparison of outcomes in adults and children is very important for improving results in both cohorts. In Italy, as in other countries, the National Transplantation Centre (NTC) has developed a separate paediatric section in the national data-base common to all ages, carrying out on a country-wide scale the data collection begun by the Paediatric Group of the North Italian Transplant Programme (NITp) in 1987 on 493 paediatric renal transplants⁴⁻⁶.

Paediatric Donor

According to Italian law, the diagnosis of cerebral disease has to be confirmed by the total absence of 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 is no major limitation on using kidneys of bigger size than those 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 Italian ones, a ratio between potential donor/recipient weight is calculated and a target ratio of >0.8 is taken into account in recipient choice. In the Italian Registry, for 231 children transplanted in the 1998-2002 period, a weight ratio < 0.8 was reported in only 17% of the cases, >0.8 < 1.2 in 25% and >1.2 in 58% of children transplants.

Renal vein thrombosis represents the major non immunological cause of renal graft loss in paediatric 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 it mostly depends on the young age and small size of the donor and particularly on the renal vessels being smaller in the donor. For these reasons donors aged less than 10 years old were reported to be reduced from 35% to 10% from 1987 to 2000 in the USA. The utilization of donors under 2 years old fell from 3.5% to 0.9%⁹ and in the UK donors < 3 year-old have not been used since 1994 and only 22% were >3 < 5 year-old in a Sick Children Hospital report in 1999. In the USA, donors aged less than 6 years old have been only used in exception circumstances, while in Italy the limit is generally for children < 2

year-old but smaller children are not excluded *a priori*, since *en-bloc* kidney transplantation may be performed. The statistics for the age of cadaveric donors (data in Italy during the observation period 1998 - 2002) is 20% of donors less than 5 years 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 of losing 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 a computer program which 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 (up to 5 year of age) and a few years for adolescents. Recent data reports that in Italy the average waiting time is 0-12 months for 71% of children needing renal transplantation, 13-36 months for 24% of children ditto and over 36 months only for 11%.

In the USA donors <18 year-old represented in 2002 some 15% of all the kidney donors and exceeded the need for the uraemic paediatric population. The waiting list is common for both adults and children and while the donations are shared among all the suitable recipients, children, however, go to the top of the list after 6-18 months of fruitless waiting. With this system in the 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 to adults (1000 days on average).

Need for renal transplantation in children

The incidence of end-stage renal failure in children has increased in the USA by 20% over the last 10 years, similar 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 years old and the five-fold increase for subjects > 65 year-old. As a result, children in the USA represent only 1.4% of patients on the waiting list, whereas ten years ago they made up 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 in January 2005, included 55 children, none under 18 months of age and under 8 kg of weight: 18% were < 5 years old, 14% were between 5 and 9 years old, 38% between 10-15 years old, and 30% were >16 years old. It is unusual for children younger than one year old to go on a waiting list either in the USA or in Italy.

The incidence of deaths while on the waiting list is particularly high for children aged less than 5 years old, who have a death incidence similar to that seen for people aged over 50 years old waiting for kidney transplantation. Whereas adults and elderly patients on waiting lists have a higher co-morbidity, the mortality of children is relevant.

Nephropathies leading to uraemia and the need for renal transplantation in children

The primary diagnosis of renal diseases leading to end stage renal failure (table I) 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 (familial nephrotic syn-

TABLE I
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 Uraemic Syndrome	3
others	36

drome, as Denis-Drash syndrome, or metabolic diseases such as primary hyperoxaluria^{11,12}. In the older age group (2-8 years) the most common are longer course hereditary diseases (such as renal polycystosis or nephronophthisis) and acquired diseases, such as focal and segmental glomerular sclerosis. In older children and particularly in adolescents the acquired nephropathies prevail over congenital forms. Amongst American black people lupus erythematosus and focal and segmental glomerular sclerosis are the more frequent cause of chronic renal failure^{13,14}.

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 a less invasive way. The

improvement of bladder and urethra reconstruction in children with neo-bladder or urethral derivation, has allowed the same survival after renal transplantation to be achieved 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 the USA, one third of which received a living related donation), is far more frequent in the USA or in Northern Europe than in Italy or in Southern Europe. The waiting list for cadaveric donor is not accessible in Italy or in most European Countries before entering chronic dialysis treatment and living donor transplantations are uncommon before dialysis. Living related transplantations (LRT), very common in the USA for a long time, have further increased over these last years. From 1987 to 2002 the percentage of LRT increased from 42% to 57%. Donors are in above 40% of the cases one of the parents, but also grandparents are common donors and over the last few years donation from unrelated donors has increased¹³. This percentage is higher than adult LRT in the USA, which is already high (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 brother⁶.

An important aspect to consider is that renal graft function cannot last for decades and the

child could need another kidney transplant. A study satellite to the ERA-EDTA Registry investigated in children who received two subsequent renal transplants whether the outcome was better when receiving first LRT or cadaver transplantation (CT). There was no significant statistical 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 the near future.

Children age at renal transplantation programming

Kidney transplantation is exceptional in children under the age of 2 years just as it is in the USA in spite of the pioneering activity of the Minneapolis Centre¹⁵ and it represents 5% of all the paediatric transplantations. Most children (80%) receive a renal transplantation when they are >6 years old. In Italy from 1987 to 1999 the median age of transplanted children was 13.7 years and only 7% was under 5 years old. More recently, in 1998-2002, an increased transplantation in the younger subjects was reported, as 21% of kidney grafts were performed on children aged between 0-5 years, 33% on children aged between 6-12 years and 48% on children aged between 16-18 years.

Renal transplantation in children aged under 2 years old has limited indications, since risk for both kidney and recipient survival was reported to be too high. Centres that began the programme of small baby transplantation - subjects

< 1 year-old weighing approx. 6 kg - more than ten years ago highlighted an increased risk of 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 weighing more than the donor¹⁵. 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 (such as the aorta, or the cava). At any rate, the choice of grafting children as young as this is exceptional and even in the 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 from peritoneal dialysis and adequate nutritional support,¹⁹ most Centres choose to wait until the child grows up to include him on the waiting list for transplantation. The risk decreases progressively and after the first year of age it is severe but not so high as to discourage the transplantation and by 18 months of age transplant success becomes likely. The risk for children older than 3 years is within the average and is not differ for adolescents.

The USA Registry NAPRTCS recently reported greatly improved results in children younger than 2 years old, but we have to consider that the number of very young babies transplanted is extremely limited and related to excellence Centres, highly specialized in this field¹⁵.

In Italy the good outcomes obtained from peritoneal dialysis and the high risk of kidney transplantation in very young children suggest waiting till the age of 18-24 months.

Surgical technique

In general, renal transplantation is technically similar in children and in adults, as anastomosis with the iliac vessels are performed in an extra peritoneal approach. In very small children the kidney is sometimes located in the 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. Just as exceptional is the *en-bloc* bilateral renal transplantation at the same time.

Extremely rare is the nephrectomy of the native kidneys, unless they are bigger due to 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 all the patients.

Immunosuppressive treatments in paediatric renal transplantation

The basal protocol of immunosuppressive treatment for paediatric renal transplantation changed in the last years. The NAPRTCS 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 the 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 the USA were on maintenance therapy with corticosteroids (C), azathioprine (AZA) and cyclosporine (CSA). Over time we have seen a revolution of this therapy for the progressive entry of new drugs and now only 15% of children are 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 side effects of therapy.

The special aim of paediatric transplantation is to reduce steroids to the minimum. C has been for a long time considered unique for rejection prevention, particularly in children. Since C selective target is cellular immunity, this drug has been considered the *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 such as transplanted children²⁷. 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 strong indications for stopping the steroid therapy due to severe clinical contraindications showed that stopping C 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 the 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. C is replaced in the first six months after transplantation, with daclizumab therapy plus TAC and MMF²¹.

CSA is still widely used in the paediatric kidney transplant. Several studies were focused on pharmacokinetics 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. The number of blood samples needed to calculate AUC make it unsuitable for children. Accordingly, the CSA blood levels at the second hour (C₂) were used, just as they are in adults. When C₂ was > 1700 ng/ml after three months, 80% of transplanted children did not have AR, versus 60% that presented C₂ < 1000 ng/ml. The target C₂ to limit chronic rejection is still under evaluation²³.

TAC aroused great interest in paediatric trans-

plantation for the possible use in 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, who received a kidney from an EBV positive donor. After a dosage reduction, the results were more satisfying and presently no increase PTLT 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 a basis of the TAC trough level, with levels around 10-15 ng/ml in the first month and decreasing to 6-10 ng/ml for maintenance. At the beginning, the comparison between TAC and CSA for the prevention of AR in paediatric kidney transplantation was in favour of TAC plus C and AZA. When AZA was replaced 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 and CSA, have similar nephro-/neuro-toxic effects, in the 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, as it has for adults, often replacing 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/m²/day. The most predicted

curve for drug exposition considers C0, C1, 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 7%). The MMF blood level measurement proved that the association with TAC produces levels allowing dosage reduction.

SIR is metabolized, as is 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 CSA 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 administered simultaneously because they do not interfere. The relevant immunosuppressive effect of SIR enhanced the search for calcineurin-free protocols²⁶. SIR significantly decreased AR incidence, and it is of particular interest both in adults and children, because of its potential antifibrosis effect in chronic allograft nephropathy (CAN). A protocol is ongoing in the USA to investigate the potential benefit of SIR on chronic rejection in children who previously experienced AR, randomized into two groups of traditional triple therapy or SIR²⁷. Over the last few years the Italian Paediatric Centres has agreed to use protocols, designed in collaboration, with the purpose of validating the outcomes of the new generation drugs, 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 in surgical procedures and knowledge of infectious and vascular complication has led to significant progress in children's 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 to 10 year-old children (Fig 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's age groups⁹. In the Italian Registry for children's renal transplantation, the survival of children less than 3 year old was 97% in the 1998-2002 period. No significant difference for patient survival are presently found in LRT and CT.

The most important causes of death in children after 10 years of transplantation include infections (33%), cardiovascular disease and neoplasm (Table II). More recent data indicate an increase in mortality due to bacterial and fungal infections and lymphoproliferative disease (PTLD)^{24,28}.

Graft survival

Over the last decade the frequency of AR dramatically reduced: the probability of AR by the first 12 months after renal transplantation, lowered 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

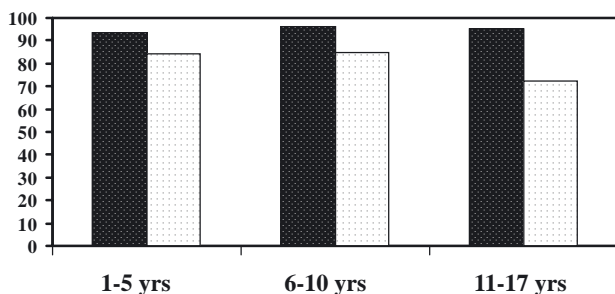


Figure 1: Graft survival at first (black column) and fifth year (white column) of living related paediatric kidney transplantation divided by age groups (2003 Annual Report USA Registry OPTN/SRTR)

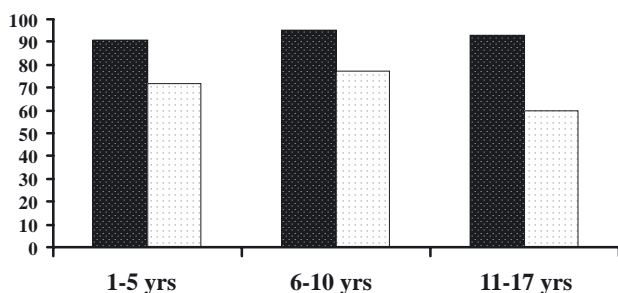


Figure 2: Graft survival at first (black column) and fifth year (white column) of cadaveric paediatric kidney transplantation divided by age groups (2003 Annual Report USA Registry OPTN/SRTR)

52% of children years ago, changed to the present 65%.

In 2002 the loss 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 of 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 to the age of the child and with the occurrence of the episode in the first year following grafting.

Also the renal survival has improved: survival at one year in the USA registry has improved over the last 5 years both in CT and 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 analysis shows CT graft survival has improved so much as to cancel the difference of graft survival with LRT. The survival improvement at one year was reflected in the survival rate of the next years: in CT three year survival increased from 50%, in the period 1980-1985 and 65% in 1986-1991, to 82% presently (Fig 2). Results are better in case of LRT: three year survival increased to 92%. The projection of renal function maintenance in children with a stable renal function at one year ($t_{1/2}$) 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 the Italian Registry had in the 1998-2002 period (for 231 children's 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-

TABLE II
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

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 weight heparins) and to the development of specific research programmes, for paediatric patients.

The general improvement in paediatric transplants is proven by the minimal need for dialysis during the post transplant period (12% in the USA) in comparison with adults (24%).

On the other hand, more recent analysis indicates worse results in the adolescents, where a poor drug compliance leads to unexpected results³¹. 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 marked decrease at 3-5 years. The reasons for these poor results are not completely clear and it seems that other factors could be involved beside non-compliance. Unexpected vascular thrombosis and the relapse of the renal disease (as Focal Segmental Glomerular Sclerosis) could be involved. At any rate the adolescent group is presently that experiencing the higher renal graft loss.

Causes of renal graft loss in children

Several causes, both immunological and non-immunological, can lead to graft loss in children. Rejection of the transplanted organ, with its different expressions, is certainly the most impor-

tant 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, as 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 include vascular thrombosis, responsible for 13% of function loss in the USA registry and particularly common when the recipient is less than 3 years old, even more when the donor is smaller than the recipient. Multivariate analysis reveal that 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 years 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; and is presently the most common acquired cause of disease in children leading to uraemia, dialysis and transplantation. This nephropathy is particularly common and aggressive in Afro-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. Afro-Americans with a very short history of disease leading to dialysis and positive result for the search of permeabilizing factor are at par-

ticular 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 lose 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 therapies proposed enjoys 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 column³², 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 uraemic 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 Erythematosus 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 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 recovery 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

TABLE III
 Causes of paediatric transplanted kidney lost
 (North Am Coop Study) 1987-1999 = 6534 paediatric
 transplants
 (*Ped Transplant 2001;5:215-231*)

	%
Primary not function	3
Trombosi vascolare	13
Tecnical 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
Other	15

worsen physical aspects of transplanted children and despondency deriving from a post-transplantation course characterized by many small to big problems. All the specialists in 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 IV) in respect to recurrent bacteria and viral infections which is the more relevant, as the immunosuppressive becomes treatment more effective. The new target of recent therapy is to reduce infections, especially CMV and HBV infections, involved in the pathogenesis of PTLD and with the risk of cancers. PTLD happens in 4.5% of the paediatric renal transplants and the RR is quadruple in comparison with adult renal trans-

plants³⁴. In a paediatric Italian study (NITp) the incidence of cancers in renal transplanted children was 2.2% in total, most were PTLD (1.3%) but also urothelial carcinoma, Wilms tumor, dysgerminoma, glioma¹⁶. The cardiovascular risk is increasingly important³⁵, due increasing the follow up in renal transplanted children, and echocardiogram is an important screening exam³⁶.

The growth

One of the most important results of the paediatric transplant is the effects on height attainment (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, uraemic-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's 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 uraemic-osteodystrophy, the correction of the anaemia, acidosis and vitamin D production exert a positive effect on the growth recovering the retardation related to uraemia³⁷. After the first year following 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 better the younger the child (< 5 years), and indeed is unsatisfactory in teenagers.

Comparing the data of children transplanted before puberty with those transplanted after, the average growth velocity increased in the first

TABLE IV
Morbidity in transplanted patients

	%
Bacterial infections	13
Viral infections	16
Hypertension	50 in the 1st year, 75 in the 3rd year
Lymphoma	2
Neoplasia	2
Post-transplant-lymphoproliferative disorders (PTLD)	2

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 puberty is significantly higher than in normal children, the total final height at puberty is lower in 20% of the cases, due to the minor length of the pubertal spurt. The final height is 1.3 SD higher in children transplanted before puberty and only 0.7 SD higher in teenagers transplanted during puberty. With current supportive therapy the final height, among the patients transplanted in paediatric age, is of normal growth of 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 closer the child is to the end of growing, the more difficult it is to obtain significant improvement.

A great interest was shown in the possibility of improving growth by using rhGH, the human recombinant hormone. This therapy was regarded with suspicion 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 immunosuppressive treatment and that could stimulate acute rejection. Clinical studies did not confirm these adverse assumptions, so the rhGH can be comparatively safely administered 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 then, 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, conducted 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 before⁴⁰.

The outcomes were satisfied: 53% worked 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. 84% thought themselves 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.

Paediatric renal transplantation needs careful therapy and scrupulous follow up. The past decade has seen substantial improvement in this treatment which is the only way to achieve a complete rehabilitation for the unfortunate child who develops a progressive chronic kidney disease.

Correspondence:

Prof. Rosanna Coppo
Nephrology Dialysis and Transplantation Unit
Regina Margherita Hospital
Piazza Polonia 94,10127, Turin
e-mail: nefrologia@iormsantanna.piemonte.it

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;3:152-67
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;1:55-60
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;7:321-35
4. SIRCHIA G, POLI F, CARDILLO M, et al. 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, PAPPALLETTERA 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, et al. Renal transplantation. Strategies to prevent organ rejection—the role of an inter-regional reference center. *Contrib Nephrol* 2005;146:1-10
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;7:204-8.
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 Arch* 2001;55:201-2.
11. SEIKALY MG, HO PL, EMMETT L, et al. Chronic renal insufficiency in children: the 2001 Annual Report of the NAPRTCS. *Pediatr Nephrol* 2003;18:796-804
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;14:2618-22.
13. NEU AM, HO PL, McDONALD RA, et al. Chronic dialysis in children and adolescents. The 2001 NAPRTCS Annual Report. *Pediatr Nephrol* 2002;17:656-63
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;72:973-8
15. KHWAJA K, HUMAR A, NAJARIAN JS. Kidney transplants for children under 1 year of age - a single-center experience. *Pediatr Transplant* 2003;7:163-7
16. GROOTHOF JW, CRANSBERG K, OFFRINGA M, et al. Dutch cohort study. Long-term follow-up of renal transplantation in children: a Dutch cohort study. *Transplantation*. 2004;78:453-60
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;18:1055-62
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;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;7:217-22
22. SILVERSTEIN DM. Risk factors for cardiovascular disease in pediatric renal transplant recipients. *Pediatr Transplant* 2004;8:386-93
23. PAPE L, EHRICH JH, Offner G. Advantages of cyclosporin A using 2-h levels in pediatric kidney transplantation. *Pediatr*

- Nephrol 2004;19:1035-8
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;8:87-90
 25. PAPE L, EHRRICH 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;18:576-9
 26. FLECHNER SM, KURIAN SM, SOLEZ K et al. De novo kidney transplantation without use of calcineurin inhibitors preserves renal structure and function at two years. *Am J Transplant* 2004;4:1776-85
 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;36:2056-7
 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;4:384-9
 29. GIPSON DS, FERRIS ME. A measure of success in kidney transplantations. *Pediatr Transplant* 2004;8:104-5.
 30. PAPE L, OFFNER G, EHRRICH JH, et al. Renal allograft function in matched pediatric and adult recipient pairs of the same donor. *Transplantation* 2004;77:1191-4
 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;6:493-9
 32. BAUM MA, Ho M, STABLEIN D, et al. Outcome of renal transplantation in adolescents with focal segmental glomerulosclerosis. *Pediatr Transplant* 2002;6:488-92
 33. SEIKALY MG. Recurrence of primary disease in children after renal transplantation: an evidence-based update. *Pediatr Transplant* 2004;8:113-9
 34. SHROFF R, REES L. the post-transplant lymphoproliferative disorder- literature review. *Pediatr Nephrol* 2004;19:369-377
 35. NOCERA A, GHIO L, DALL'AMICO R, et al. De novo cancers in paediatric renal transplant recipients: a multicentre analysis within the North Italy Transplant programme (NITp), Italy. *Eur J Cancer* 2000;36:80-6
 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;56:1566-70
 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;8:357-61
 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;62:688-96
 39. ACOTT PD, PERNICA JM. Growth hormone therapy before and after pediatric renal transplant. *Pediatr Transplant* 2003;7:426-40
 40. BARTOSH SM, LEVERSON G, ROBILLARD D, SOLLINGER HW. Long-term outcomes in pediatric renal transplant recipients who survive into adulthood. *Transplantation* 2003;76:1195-200