Prevention, diagnosis and therapy of transplant nephropathy in children

Lars Pape, Offner Gisela and Jochen HH Ehrich

Hannover, Germany

Background: **In recent years transplant nephropathy has become the predominant cause of graft failure in children. Therefore, the new methods of prevention, diagnosis and therapy need to be critically evaluated.**

Methods: **The methods include evaluation of long term graft function by Doppler ultrasonography, histological quantification of tubulointerstitial fibrosis, pharmocokinetic monitoring of immunosuppression, allocation of donor kidneys, and use of new immunosuppressive regimen.**

Results: **In a matched-pairs-analysis of the function of kidneys taken from adult donors was inferior to that of pediatric donor kidneys, thus showing the superiority of the "young for young" concept of organ donation. The quantification of fibrosis with PicroSiriusRed staining in renal biopsies correlated positively with the progression of graft failure revealing a new predictor of future graft function. Renal resistance indices >0.8 were identified as risk factors for loss of graft function. The advantages of C_2-cyclosporin A level monitoring in comparison to conventional C_0-monitoring was shown and C_2 target levels were given. Basiliximab, an IL2-receptor-antagonist, had a positive effect on prevention of acute rejection episodes.**

Conclusions: **Long-term kidney transplant function and survival can be improved by a combination of well directed prophylaxis, early diagnosis and an individually tailored immunosuppressive therapy.**

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Key words: **transplant nephropathy; kidney transplantation; chidren; prevention; therapy**

Author Affiliations: Department of Pediatric Nephrology, Hepatology and Metabolic Diseases, Hannover Medical School, Hannover, Germany (Pape L, Offner G and Ehrich JHH)

Corresponding Author: Lars Pape, MD, Department of Pediatric Nephrology, Hepatology and Metabolic Diseases, Medical School of Hannover, Carl-Neuberg-Strasse 1, D-30625 Hannover, Germany (Tel: +49-511-532-3213; Fax: +49-511-430-4839; Email: pape.lars@mh-hannover.de / ehrich.jochen@mh-hannover.de)

Introduction

Thirty-five years ago, children with end-stage renal failure could not survive in most countries. But modern pediatric dialysis regimens have made kidney replacement therapy possible. As a therapy of choice for pediatric chronic renal failure, kidney transplantation replaces the time-consuming and psychologically debilitating dialysis therapy and promises normal growth and positive psycho-social development.[1]

In earlier decades, prevention and therapy of acute rejections were major challenges to pediatric renal transplantation. But new immunosuppressive medication and regimens reduce acute rejection in less than 20% of patients during the 1st year. The one-year graft survival rate can be 95% whereas the long-term survival remains unchanged.[2]

Transplant nephropathy (TN), the main factor for the decline of long-term kidney transplant function,[3] is the sum of different immunological factors such as human leucocyte antigen (HLA) mismatches, medication non-compliance, unstable blood levels of immunosuppressive medication, viral infection and non-immunological factors such as tissue damage due to reperfusion, hyperlipidemia, arterial hypertension, proteinuria and calcineurin-inhibitor toxicity.[4]

Multiple factors must be taken into consideration in order to prevent chronic loss of kidney transplant function. The selection of suitable donors is one of the factors for reducing TN. Using living related donors / parents (LRD) leads to a longer graft survival because of a short time of cold ischemia. Thus LRD should be considered initially (Fig. 1).

In many cases, however, living donation is not possible. Up to now, it is unclear whether pediatric recipients benefit from the allocation of adult or pediatric kidneys based on the hyperfiltration theory.[5] Furthermore, it is unclear to what extent the progress of TN may be stopped or reversed by changes in the immunosuppressive therapy. Scoring-systems of TN are based on interstitial fibrosis, vascular and glomerular changes.[6] Early interstitial fibrosis

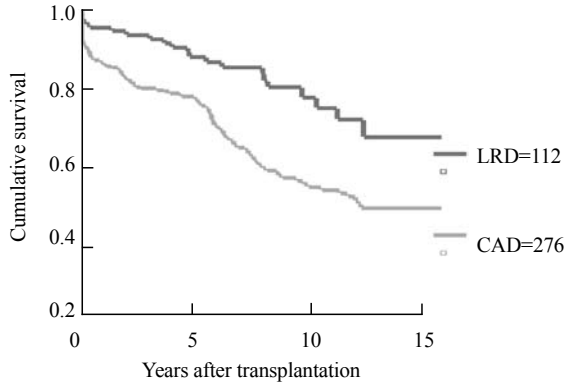

Fig. 1. The kidney transplant survival of children who had received organs from living related donors (LRD) or cadaveric donors (CAD) in Hannover, Germany since 1985.

within the early months after transplantation is a reliable surrogate marker for TN. Semi-quantitative methods are used to obtain the amount of interstitial fibrosis. Different pathologists examining the same preparation may find different results about the amount of fibrosis.[7] Quantitative methods are rarely effective in detecting interstitial fibrosis, but PicroSiriusRed can be used as a marker in intestinal fibrosis, because its intercalation with collagen fibers I and II. The amount of intestinal fibrosis can be calculated by a computer-associated image analysis system. The correlation of intestinal fibrosis quantified by computer associated image analysis and changes in glomerular filtration rate (GFR) in children with advanced TN has been investigated over a period of two years.

The resistance index (RI) of segmental arteries after kidney transplant is a further reliable predictor of transplant function.[8] But it is still unclear whether a correlation between RI and intestinal fibrosis exists and whether the progression of TN could be predicted reliably by a combination of both methods.

Using cyclosporin A (CsA) as an immuno-suppressant and trough level monitoring leads to better long-term transplant survival rates.[9] The "area under the curve concentration" (AUC) is correlated better with CsA 2-hour-levels (C_2) than with C_0.[10] Because C_2-target-levels in pediatric kidney transplantation are still unknown, the effect of C_2-based monitoring of CsA in children has not been studied so far.

IL-2-receptor antagonists like basiliximab, a human-murine antibody, in combination with CsA reduces significantly the chance of acute rejection in adult kidney transplantation significantly.[11] No data from controlled studies are available on long-term transplant function and side-effects of this regimen in children.

In this article we summarized our previous findings,[12-18] while addressing the following questions:

1. Can progression of TN be influenced by age equivalent cadaveric donor (CAD) kidneys?
2. Are the quantification of intestinal fibrosis by PicroSiriusRed and the measurement of renal resistance index sufficient for predicting transplant function and early indicators for possible changes in immunosuppressive therapy?
3. Which target levels of C_2 should be reached in pediatric kidney recipients?
4. Is C_2-monitoring superior to conventional trough level monitoring in improving long-term transplant function?
5. Does additional induction therapy with the IL-2-receptor antagonist basiliximab lead to better transplant function? What are the associated risks?

Methods

Selection of donors / "matched-pairs-analysis" in cadaveric donors[12]

Of the Eurotransplant population, 15 cadaveric donors were selected. One of the 15 kidneys was allocated to a pediatric recipient and one to an adult recipient. Over 7 years, 15 pairs of recipients could be defined ("matched pairs") and were retrospectively analyzed. There were 9 adults (median age 40 years, range 23-60 years) and 6 pediatric donors (median age 11 years, range 4-15 years) among the 15 cadaveric kidney donors. All recipients had received a comparable immunosuppressive therapy including prednisolone, cyclosporin A, and azathioprine. The number of acute rejections, cytomegaly virus reactivations and antihypertensive medications was comparable. The mean ages of pediatric and adult recipients were 5 years (range 1-9 years) and 38 years (range 25-60 years), respectively. The development of serum creatinine, body surface correlated relative GFR (calculated by Schwartz[19]), and the calculated absolute GFR were compared over a period of seven years.

Computer-associated quantification of intestinal fibrosis by PicroSiriusRed[13]

After a median time of 3.8 years following transplantation (range 1.0-10.6 years), biopsies were carried out because of a significant rise in creatinine in 56 pediatric recipients (median age 9.4 years, range 1.4-15.1 years). After the biopsy, all patients received mycophenolat mofetil (MMF) in addition to prednisolone and cyclosporin A. The specimens of biopsies were stained with PicroSiriusRed. By polarisation microscopy (Olympus AX70) with an integrated digital camera, a picture of the cortex

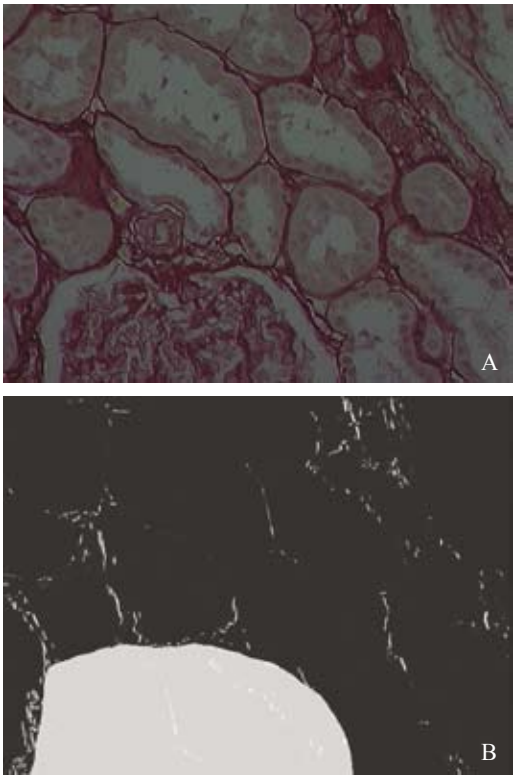

Fig. 2. Paraffin section of the renal cortex stained with PicroSiriusRed. **A:** without polarisation, **B:** under polarized light, and glomerulum excluded.

of each kidney biopsy was taken. Glomerula were subtracted afterwards (Fig. 2). The amount of intestinal fibrosis was measured by computer-associated image analysis (Scion Image, Scion Corporation, Frederick, MD, USA). A linear regression analysis was made between the amount of cortical intestinal fibrosis and changes in GFR both during biopsy and 2 years later.

Measurement of renal resistance index[14,15]

One year after transplantation and at the time of biopsy, the minimal diastolic and the maximal systolic flow in the two segmental arteries of kidney transplant of the same patients (undergoing the above-mentioned biopsies) were measured with a Philips ATL HDI 5000 system consisting of a 2-4 MHZ segmental scanner and a 2.5 MHz doppler. RI was calculated according to RI=100 × [1-(Vmin/Vmax)].

Determination of cyclosporin A 2-hour target levels in pediatric recipients one year after transplantation[16]

The C_2 levels of 102 patients (mean age 12±5 years, 43 LRD, 58 CAD) were measured by EMIT-Assay, the earliest stage being one year after transplantation (mean time after transplantation 5.3±1.9 years). The immunosuppressive therapy with prednisolone, CsA and also additional MMF was given to 40 patients. CsA dosages were adjusted according to CsA trough levels every 2-4 weeks (trough target level of 100-150 ng/ml). GFR, calculated according to Schwartz, was compared three times: six months before the switch from C_0 to C_2 monitoring, at the time of the switch, and six months thereafter.

Regulation of cyclosporin A dosage by C_2 target levels[17]

At one year after transplantation (mean time after transplantation 7.0±5.6 years), 49 pediatric kidney transplant recipients (mean age 12±5 years, 21 LRD, 28 CAD) were changed from C_0 to C_2 monitoring. The target level for C_0 monitoring was 100 ng/ml. After changing to C_2 monitoring, the CsA dosage was adapted by C_2 levels over 1000 ng/ml or under 700 ng/ml. GFR, according to Schwartz, had been calculated six months before the switch to C_2 monitoring, at the time of the switch and six months thereafter. Furthermore, the coefficient of the variation of six C_0 and C_2 levels was compared.

Induction therapy with basiliximab[18]

From June 1997 through June 2000, 77 children between 0.5 and 16 years received 78 kidney transplants. Among them, 48 pediatric recipients (median age 7.8±5.3 years, 10 LRD and 19 CAD) received an immunosuppressive therapy with prednisolone, CsA and basiliximab as induction (day 0 and day 4). A control group of 29 children (10 LRD, 19 CAD, mean age 7.3±5.2 years) was treated without basiliximab. The development of GFR, according to Schwartz, CsA dosages, CsA trough levels, side-effects of basiliximab therapy, and the number of acute rejections, was observed over a period of three years.

Results

Matched-pairs-analysis[12]

The initial GFR, calculated according to Schwartz and correlated to body surface, did not differ in pediatric and adult recipients independent of received donor kidney type (adult or pediatric). During evaluation, the mean GFR of pediatric recipients was significantly higher in transplantation of pediatric than in adult donor kidneys. Also, during the final years of observation, serum creatinine levels were lower in children who had a pediatric transplant than in those with an adult donor kidney. The initial absolute GFR, independent of donor type, was significantly lower (P<0.05) in pediatric

recipients (median GFR 27 ml/min, range 17-38 ml/min) than in adult recipients (median GFR 54 ml/min, range 25-74 ml/min) and kept lower throughout the following years. Through out the observation time, the kidneys of adult donors transplanted to pediatric recipients had a lower GFR than those transplanted to adult recipients, whereas the transplanted kidneys of pediatric donors were not different in GFR between adult and pediatric recipients (Fig. 3).

Computer-associated quantification of intestinal fibrosis by PicroSiriusRed[13]

In two years after biopsy, the fraction of PicroSiriusRed positive cortex volume (V_{IntFib}) at the time of biopsy was correlated significantly (r = 0.61, P<0.001) with the decline in GFR (Fig. 4).

Eighty-five percent of patients with V_{IntFib}<5% had a rising GFR, whereas 93% of patients with V_{IntFib}>10% had a declining GFR within two years. V_{IntFib} differed significantly (P=0.008) between patients with a stable GFR and those with a declining GFR.

Renal resistance index and cortical fibrosis[14,15]

RI one year after transplantation correlated significantly with RI at the time of biopsy (r=0.58, P<0.01). V_{IntFib} was higher in children with RI≥80 than in those with RI<80 (mean V_{IntFib}=9.5±3.2% vs 5.2±5.1%; P=0.004). In children with V_{IntFib}>10%, mean RI was 77±5 compared to 69±6 in patients with V_{IntFib}<10% (P=0.0002) (Table 1). The highest predictive value for determining the risk of declining GFR of more than 5% over 2 years after biopsy was seen in 89% of patients whose RI≥80 was associated with V_{IntFib}>10%. If only V_{IntFib}>10% or only RI ≥80 was present, the predictive value was 87% and 67% (Table 2).

Cyclosporin A 2-hour target level[16]

The median C_2-level of all patients was 714 ng/ml (95%, range 654-774 ng/ml) and the median C_0-level was 112 ng/ml (95%, range 101-123 ng/ml). There were no significant differences between subpopulations with or without MMF-therapy. The median CsA dosage was 145 mg/m² per day (95%, range 140-50 mg/m² per day).

After six months, a higher percentage of decline in GFR was seen in children with C_2 levels <750 ng/ml than in those with C_2 levels >750 ng/ml (P<0.05, the Mann-Whitney U test). No significant difference in GFR was observed in patients with C_2-levels >1000 ng/ml and those with C_2-levels between 750 and 1000 ng/ml. Moreover, after splitting into the two groups

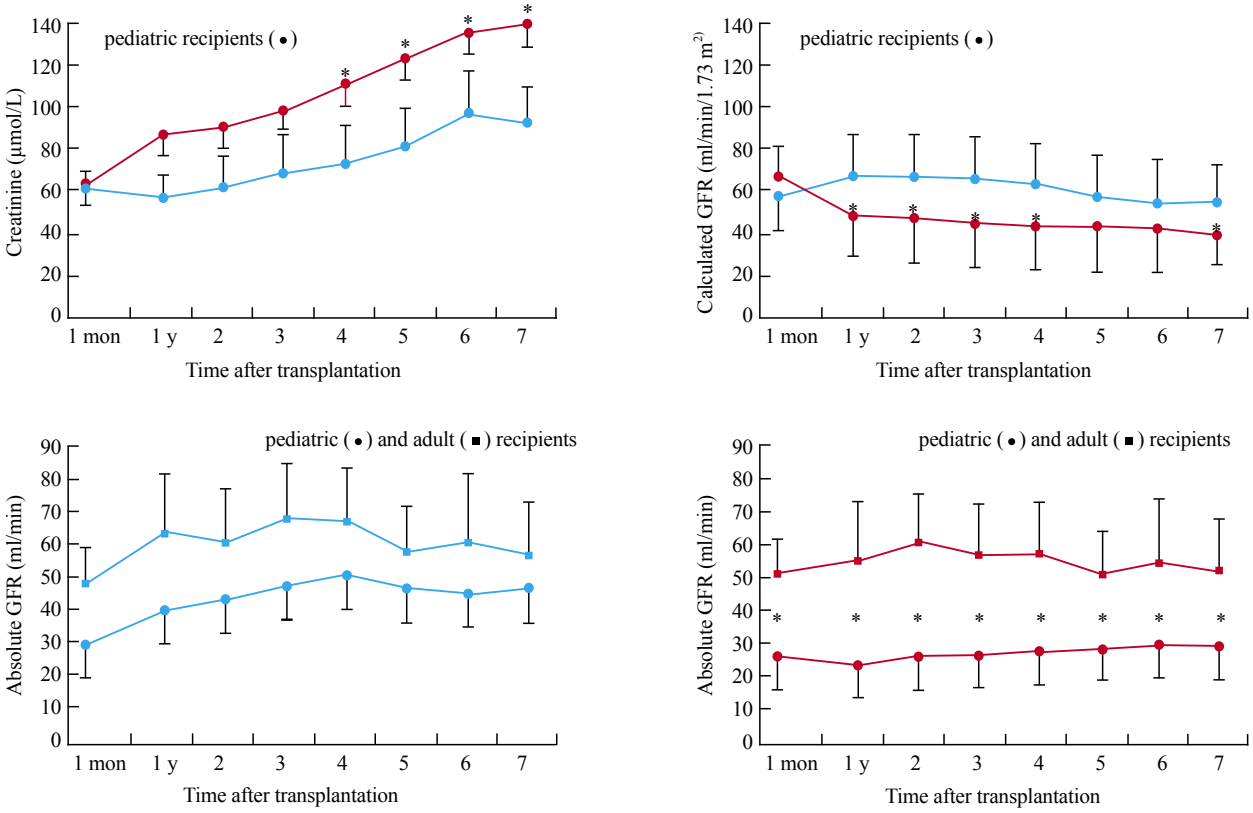

Fig. 3. Creatinine, calculated GFR after Schwartz and absolute GFR in pediatric (•) and adult (■) donors, who received a kidney from adult or pediatric donors, over 7 years. Red color represents pediatric donors, blue represents adult donors (*: P< 0.05).

with different C_0 levels, no difference was seen in GFR development (Table 3). Only three acute rejections occurred in children with C_2 levels <500 ng/ml two, three, and ten years after transplantation (P<0.05, the chi-square test).

Cyclosporin monitoring based on C_2-levels[17]

The mean CsA dosages were 308±119 mg/m² per day, 294±105 mg/m² per day and 289±158 mg/m² per day, six months before, at the time of, and six months after the switch from C_0 to C_2 monitoring, respectively. These differences in CsA dosage were not statistically significant. The mean C_0 levels were 95±38 ng/ml and 106±41 ng/ml six months before and at the time of the switch, respectively. At the time of the switch, the mean C_2 level was 701±246 ng/ml, in contrast to 630±176 ng/ml six months after the switch. There were no statistically significant differences between CsA dosage and C_0 level in patients with and without additional MMF therapy (C_0-levels: 641±169 vs 589±196 ng/ml, P>0.05, unpaired t test; CsA dosage: 295±109 vs 285±170 ng/ml).

During C_0 monitoring, 23 dosages were modified for 16 patients (16 with MMF therapy) but 25 dosages were modified for 19 patients (13 with MMF) after the switch to C_2 monitoring. GFR declined in 33 patients (25 with MMF) and increased in 16 patients (12 with MMF) during the 6 months of C_0 monitoring. In the subgroup with C_2 monitoring, GFR declined in 23 children (17 with MMF) and increased in 26 children (20 with MMF).

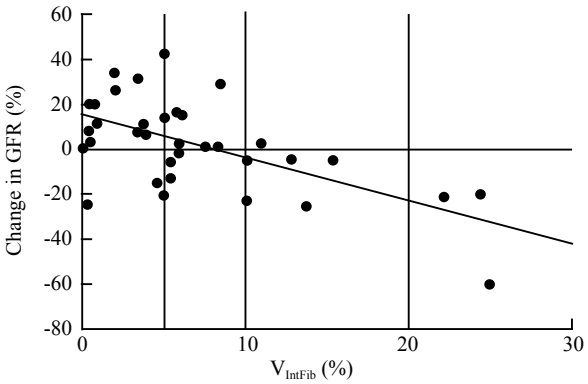

Fig. 4. Regression analysis between the PicroSiriusRed positive fraction of the cortex (V_{IntFib}) and the change of GFR, r=0.62, P<0.001.

Table 1. Relation between the PicroSiriusRed positive fraction of the cortex in the transplanted kidney (V_{IntFib}) with the renal resistance index (RI) at time of biopsy

	mean V_{IntFib}±SD (%)	
RI<80	5.2±5.1	
RI≥80	9.5±3.2	P=0.004
	mean RI±SD	
V_{IntFib}<10%	77±5	
V_{IntFib}>10%	69±6	P=0.002

Table 2. Sensitivity, specifity, positive and negative predictive value, relative risk and odds ratio (%) of renal resistance index (RI) and fraction of PicroSiriusRes positive fraction of renal cortex (V_{IntFib}) for the prediction of an increase or decrease in glomerular filtration rate (GFR) two years after renal biopsy

	Sensitivity	Specifity	Positive predictive value	Negative predictive value	Relative risk ratio	Odds
End point: decrease of GFR of more than 5%						
RI≥80	30	86	67	61	1.7	3.2
V_{IntFib}>10%	30	95	87	49	1.9	8.2
RI≥80 and V_{IntFib}>10%	22	99	98	55	2.4	113.2
End point: decrease of GFR of more than 5%						
V_{IntFib}<5%	65	83	81	53	2.6	9.3
RI<8	86	30	61	67	1.8	3.2
V_{IntFib}<5% and RI<80	67	88	88	68	2.8	15.0

Table 3. Changes in glomerular filtration rate (GFR) within 6 months in groups of pediatric graft recipients with different C_0- and C_2-levels, median values and 95% confidence intervals

C_2-level (ng/ml)	C_0-level (ng/ml)	GFR-change (%)	CsA-dose (mg/m²/d)	n
<750	91 (73-109)	-7.4 (-12.6-2.2)	136 (110-163)	53
>750	136 (110-163)	-1.8 (-7.2-3.6)	185 (149-221)	48
>1000	156 (126-186)	-1.7 (-4.2-0.9)	210 (169-251)	19
C_0-level (ng/ml)	C_2-level (ng/ml)	GFR-change (%)	CsA-dose (mg/m²/d)	n
<100	527 (403-624)	-4.7 (-3.8-5.6)	160 (129-191)	39
>100	898 (723-1073)	-5.9 (-7.0-4.8)	200 (151-239)	62
>150	1008 (811-1205)	-4.3 (-5.1-3.5)	210 (159-251)	38

The mean calculated GFR was 53±15 ml/min/1.73 m^2 six months before the switch, but declined to 49 ±12 ml/min/1.73 m^2 at the time of the switch. It was stable over the six months when C_2 monitoring was used (49±15 ml/min/1.73 m², P=0.5, paired t test), independent of MMF co-medication. The percentage of change in GFR was calculated individually for each patient. The average decline in GFR was -3.7±7.7% by C_0 monitoring and 0.7±6.0% by C_2 monitoring (P=0.01, unpaired t test).

All patients whose CsA dosage was reduced by more than 5% (n=6 with MMF and n=3 without MMF) showed an increasing GFR of 3.9±7.9% over the six months of C_2 monitoring. The median coefficient of variation between intra-individual C_0 levels was 0.31±0.15 which was significantly higher than that between C_2 levels (0.24±0.1, P=0.02, unpaired t test). No acute rejections were seen over the whole time of investigation (Table 4).

Induction therapy by basiliximab[18]

The one-year transplant survival rate was 95% in patients receiving basiliximab which was similar to that in the control group (93%). Acute rejections were fewer in children using basiximab than in those receiving induction therapy (14% vs 34%, P<0.05, the chi-square test). At the time of discharge after transplantation, the calculated GFR was higher in patients receiving basiliximab therapy than in those untreated (66 vs 52 ml/min/1.73 m², P<0.05, the Mann-Whitney U test). The higher GFRs of patients receiving basiliximab were associated with higher C_0 levels (214 vs 174 ng/ml, P<0.05, the Mann-Whitney U test). One year after transplantation, GFR was comparable in both groups (58 vs 52 ml/min/1.73 m², P>0.05, the Mann-Whitney U test). In Fig. 5, transplant survival and cumulative percentage of acute rejections of these patients are demonstrated.

Twenty-four percent of patients receiving basiliximab therapy were hospitalized because of

Table 4. Results of switch from C_0- to C_2-monitoring

	C_0-monitoring	Switch to C_2	C_2-monitoring
Mean GFR (ml/min/1.73 m²)	53±15	49±12 *	49±15
GFR-change (%)		-3.7±7.6 *	0.7±6.7
Mean CsA-dose (mg/d)	308±119	294±105	289±159
Change of CsA-dose (%)	-3.3±9.4	0.4±12.5 *	
Coefficient of variability of C_0-/C_2-levels		0.3±0.2	0.2±0.1

Percentual change of glomerular filtration rate (GFR) in children with a reduction of CsA-dose >5% (n=9) after switch to C_2-monitoring: 3.9±7.9 ml/min/1.73 m² (*: P<0.05).

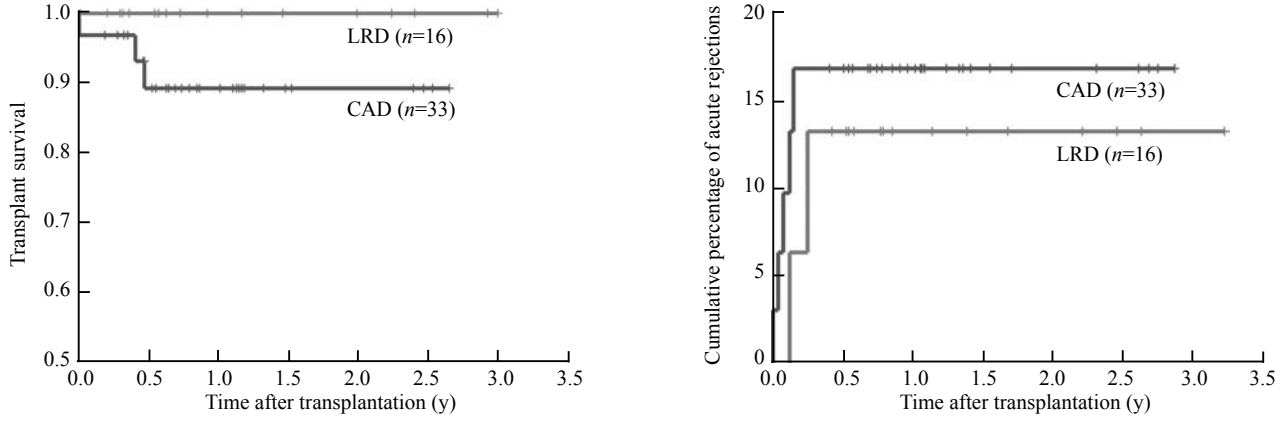

Fig. 5. Transplant survival and cumulative percentage of acute rejections in LRD (n=16) and CAD-organs (n=33) in 49 transplanted children, treated with basiliximab, prednisolone and cyclosporin A.

infection and 34% untreated with basiliximab were also hospitalized. Before transplantation, 29% patients were CMV-IgG positive in the basiliximab group and 24% EBV-IgG positive versus 48% and 65% in the control group. After the first year of transplantation, 6% of the patients treated with basiliximab developed CMV-IgM (2 seroconversions, 1 reactivation) versus 21% in the control group (4 seroconversions, 2 reactivations). EBV-IgM was seen in 20% of patients treated with basiliximab (7 seroconversions, 3 reactivations) compared to 7% in patients untreated with basiliximab (2 seroconversions). No patients developed post transplant lymphoproliferative disease after transplantation. All the 77 patients who had been treated with basiliximab survived the time of investigation.

Discussion

Prevention of chronic allograft nephropathy[12]

A progressively declined function of renal transplant in adult recipients because of continuous hyperfiltration of nephrons was described by Brenner hypothesis. Brenner also found that a better long-term renal function could be expected in pediatric patients receiving adult donor kidneys who experience no hyperfiltration because of the lower need of pediatric recipient and that deactivated nephrons of the adult donor transplant could be "activated" or the rate of filtration per nephron increases during the time of growth.

Our results do not support these hypothesis. In our study, however, GFR was not increased in pediatric patients receiving adult donor kidneys over the years after transplantation. Rather, there was a worse clinical outcome compared to children receiving pediatric donor kidneys. On the other hand, pediatric donor kidneys had a comparable function—whether transplanted in pediatric or adult recipients. These results could be explained by the following concept that the GFR of an adult kidney transplanted to pediatric recipients is lower than that of the remaining single kidney of the adult donor which have been transplanted into an adult recipient, thus a functional adaptation of GFR to pediatric organism can be postulated.[20] Hypofiltration in adult kidney transplants after transplantation into children is not reversible. The "Senescence-Concept" is therefore an important explanation for these changes.[21] Young kidneys may show less acute tubular necrosis and few other aging processes, and therefore may adapt better to the needs of a growing organism.[22] Accordingly, these kidneys can raise their filtration rate over the years parallel to the growth of the patient.[23]

Hence, kidneys of younger donors aged from 4 to 26 years should be preferentially allocated to pediatric recipients.[24] This strategy is adapted in France, USA, Spain and UK. Because of the lack of pediatric donors, adult kidneys need to be accepted for children when pediatric kidney is not available.

Diagnostic procedures[13-15]

A cortical fraction of PicroSiriusRed (Vfib) stained tissue for over 10% was a significant surrogate marker of decline in GFR of a kidney biopsy within two years. V_{Fib} less than 5% identified a subgroup of patients whose renal function can be improved by changes of immunosuppressive therapy. The coefficient of correlation between PicroSiriusRed (as a single method of biopsy analysis) and development of TN was exceptionally high, indicating that TN is a multifactorial process of many factors such as non-compliance, acute rejection, and arterial hypertension. These factors play a role in the decline of renal function. This method is advantageous in high reliability because of computer-associated image analysis, which is independent of examiners.

PicroSiriusRed staining can not distinguish pre-existing (of donor) from newly appearing fibrosis (of recipient). Biopsies at transplantation ("zero-biopsy") should be performed to detect newly developed fibrosis by subtracting the fibrosis levels of "zero-biopsy". This would make the method more informative, but unsolved is the problem of "sampling errors" (the incidental biopsy of a non-representative part of kidney transplant).

We found that a high RI≥80 of segmental arteries of transplanted kidneys is an early and easily obtainable parameter in predicting a decline of renal function. The positive predictive value of RI≥80 in pediatric recipients was not as high as in adult ones[8] because children have fewer typical risk factors such as arterial hypertension or diabetic nephropathy, which are the main factors declining renal function in adults. The combination of both methods (quantification of fibrosis by PicroSiriusRed and RI) can significantly improve the predictive value. The combination of RI≥80 and V_{IntFib}>10 % showed a positive predictive value of 98% for the decline of renal function over the next 2 years. On the other hand, the combination of RI<80 and V_{IntFib}<5% identified a subgroup of kidney transplanted children whose GFR was increased when they received additional MMF after the biopsy showing TN. Both methods were highly correlated. Most patients with RI≥80 had a high level of fibrosis, and those with V_{IntFib}>10% had a high RI. An independent predictive value for the combination of both methods was detected

by the high combined-odds-ratio of both methods, which was significantly higher than that of individual method. With V_{IntFib}, the amount of cortical fibrosis in TN can be explained by severity of macrovascular changes and other factors such as calcineurin toxicity, acute and chronic rejections. RI as a marker for microvascular changes, particularly is peritubular capillaries, represents an independent vascular factor of TN.[25]

PicroSiriusRed staining and RI measurement, in particular when combined, are two easy, fast, and inexpensive methods to predict renal function in TN and to decide the time for change of immunosuppressive therapy. We recommend these methods as standard procedures in combination with established scores such as the Banff-Score.

Therapy[16-18]

In out study, a target C_2 level of 750-1000 ng/ml was identified in stable pediatric renal recipients. The level below 750 ng/ml was related to a significantly higher risk of acute rejection. Non-compliance causing acute rejection could not be ruled out in our patients, however, stable trough levels of 80-100 ng/ml in these patients made non-compliance unlikely.

Increasing CsA toxicity and malignancies were described for C_2-levels over 1000 ng/ml.[26] We found that a decline in GFR could be stopped by switching C_0 monitoring to C_2 monitoring. Over-immunosuppression in some children under trough level monitoring seems to play a decisive role in this model. When the CsA dosage was reduced by over 5% under C_2 monitoring, GFR was increased, indicating another advantage of C_2 monitoring: a low coefficient of variability. This coefficient of variability was significantly lower than that under C_0 monitoring of CsA microemulsion (0.28 ±0.06 vs 0.41±0.06).[27] The intra-individual coefficient of variability was also significantly lower after the switch of C_0 to C_2 monitoring. This low variability of C_2 monitoring was probably influenced by the interval of time to draw blood (2 hours after CsA intake ±5 min). We suggested that an ambulant C_2 monitoring as routine is practicable. Long-waiting period or tardy patients are secondary problems in a well-organized outpatient unit.

Ambulant C_2 monitoring of CsA dosage is safe and can routinely be performed in long-term kidney transplanted children, resulting in less loss of renal function by detecting over-immunosuppressed patients. Thus, randomized studies on C_0 and C_2 monitoring after transplantation should be carried out.

Additional induction therapy with basiliximab in pediatric recipients can reduce the number of acute rejections. The rates of acute rejections are lower than those in the North American NAPRTCS data base[28] and those of adult recipients.[11] The treatment with basiliximab also leads to an excellent one-year-transplant-survival-rate. In our study, GFR remained stable over the first year post transplantation. The acutely decreasing CsA-levels, which were associated with rising serum creatinine, could be caused by interaction between basiliximab and CsA during the first month after transplantation.[29] This interaction could also explain why a low GFR in the basiliximab group was seen at the time of discharge. No infections were seen while using basiliximab.

Despite the long-term data of randomized studies are still pending, we conjectured that an induction therapy with basiliximab in pediatric renal transplant recipients reduces the number of acute rejections after transplantation.

Conclusions

Long-term transplant function, the quality of life and survival of pediatric renal grafts can be improved by a combination of well directed prophylaxis, early diagnostic investigations and an individual immunosuppressive therapy. Long-term graft function can be achieved by allocating pediatric donor kidneys to pediatric recipients, early diagnosis of TN by quantification of fibrosis using PicroSiriusRed staining, measurement of RI and improvements in the immunosuppressive therapy such as CsA drug monitoring by CsA 2-hour-levels instead of trough levels.

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Competing interest: None declared.
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